AMERICAN ACADEMY OF PEDIATRICS

Quick Reference Guide to Pediatric Care

2ND EDITION

KAMAT

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American Academy of Pediatrics

DEDICATED TO THE HEALTH OF ALL CHILDREN®

AMERICAN ACADEMY OF PEDIATRICS

Quick Reference Guide to Pediatric Care

2ND EDITION

Deepak M. Kamat, MD, PhD, FAAP
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Facsimile: 847/434-8000
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Preface

It is an honor and privilege to present the second edition of the *American Academy of Pediatrics Quick Reference Guide to Pediatric Care.* Medical knowledge is expanding rapidly and it is difficult to keep up with it, especially for busy practitioners taking care of children during their daily practice. The *American Academy of Pediatrics Quick Reference Guide to Pediatric Care* is the go-to reference for everyone taking care of children, providing them with the information they need while seeing patients or between appointments without having to sift through mounds of information.

This trusted resource contains nearly 200 topics from the Point-of-Care Quick Reference of the American Academy of Pediatrics (AAP) online resource *Pediatric Care Online*™ (www.pediatriccareonline.org). Succinctly displayed in a bulleted format, the content covers key aspects of pediatric care: screening, treatment, signs and symptoms, emotional and behavioral problems, and specific clinical problems.

The content in this publication was culled from the following best-selling AAP resources:

- *Pediatric Care Online*
- *American Academy of Pediatrics Textbook of Pediatric Care,* 2nd Edition
- *Red Book®: 2015 Report of the Committee on Infectious Diseases,* 30th Edition
- *Bright Futures: Guidelines for Health Supervision of Infants, Children, and Adolescents,* 4th Edition

I would like to extend my sincere thanks to all the authors and editors of these AAP resources.

I am grateful to many individuals at the AAP who encouraged and supported me in the production of this second edition. My sincere thanks to Ms Jennifer McDonald, manager, online content at the AAP, for her dedication and commitment in getting this second edition published on schedule. I could not have done this without the support of my wife, Dr Ambika Mathur, and my children, Dr Amol Kamat and Dr Aarti Kamat, for putting up with me as I worked late nights and weekends, editing to meet the deadline for this publication.

It is our hope that the *American Academy of Pediatrics Quick Reference Guide to Pediatric Care,* 2nd Edition, will be the standard point-of-care reference for everyone who takes care of children, including pediatricians, pediatric residents, and medical students alike, as they strive to provide the best care possible for infants, children, adolescents, and young adults all over the world.

Deepak M. Kamat, MD, PhD, FAAP

Editor in Chief

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Abdominal Pain

DEFINITION

- *Abdominal pain* is defined as pain perceived to be in the area of the abdomen (between the thorax and pelvis).
- Functional abdominal pain (FAP) is the most common cause of chronic abdominal pain in the pediatric population.
  - Occurs ≥3 times over ≥3 months and is severe enough to affect daily activities in children >3 years.
  - According to Rome III criteria, FAP must include all of the following characteristics:
    1. Episodic or continuous abdominal pain
    2. Insufficient criteria for other functional gastrointestinal (GI) disorders
    3. Absence of an inflammatory, anatomic, metabolic, or neoplastic process that explains symptoms disorders
  - Rome III criteria for functional bowel disorders associated with abdominal pain or discomfort in children are
    1. Functional dyspepsia
    2. Irritable bowel syndrome
    3. Childhood FAP
    4. Abdominal migraine
  - Usefulness of the Rome III criteria remains to be established.

HISTORY

- History accounts for most of the data used in making a diagnosis.
  - Location, onset, and severity of pain
  - Alleviating and precipitating factors
  - Associated symptoms
  - Timing of onset, changes in intensity, location, and quality of pain over time
  - Effect of pain on school, work, sleep, and mood
  - Family history
  - Patient medical history
  - Environmental and behavioral factors
- Children with FAP are more likely to have headache, joint pain, anorexia, vomiting, nausea, excessive gas, and altered bowel symptoms.
- Alarming symptoms that may suggest higher probability of nonfunctional disease
  - Involuntary weight loss
  - Deceleration of growth
  - GI blood loss
  - Significant vomiting
  - Chronic severe diarrhea
  - Persistent right upper or right lower quadrant pain
  - Unexplained fever
  - Family history of inflammatory bowel disease

PHYSICAL EXAMINATION

- Complete physical examination should be performed in all initial assessments of abdominal pain, including
  - Urethral orifice
  - Vaginal orifice
  - Rectal examination
- Most children with FAP will have normal findings.
  - Normal examination and absence of alarm signals point toward diagnosis of functional pain.

DIFFERENTIAL DIAGNOSIS

Acute Abdominal Pain by Age

- Neonate
  - Necrotizing enterocolitis
  - Spontaneous gastric perforation
  - Hirschsprung disease (congenital megacolon)
  - Meconium ileus
  - Intestinal atresia or stenosis
  - Peritonitis from gastroschisis or ruptured omphalocele
  - Traumatic perforation of viscus (difficult birth)
- Infant (<2 years)
  - Colic (<3 months)
  - Acute gastroenteritis or viral syndrome
  - Traumatic perforation of viscus (child abuse)
  - Intussusception
  - Incarcerated hernia
  - Volvulus (malrotation)
  - Sickling syndromes
- School age (2–13 years)
  - Acute gastroenteritis or viral syndrome
  - Urinary tract infection
  - Appendicitis
  - Trauma
  - Constipation
  - Pneumonia
  - Sickling syndromes
- Adolescent
  - Acute gastroenteritis or viral syndrome
  - Urinary tract infection
  - Appendicitis
  - Trauma
  - Constipation
  - Pelvic inflammatory disease
  - Pneumonia
  - Mittelschmerz

A

Chronic Abdominal Pain by System

- GI tract
  - Gastroesophageal reflux disease
  - *Helicobacter pylori* gastritis
  - Peptic ulcer
  - Esophagitis
  - Lactose intolerance
  - Celiac disease
  - Parasitic infection (*Giardia, Blastocystis hominis*)
  - Inflammatory bowel disease
  - Meckel diverticulum
  - Malrotation with intermittent volvulus
  - Chronic appendicitis
  - Constipation
- Gallbladder, liver, and pancreas
  - Cholelithiasis
  - Choledochal cyst
  - Hepatitis
  - Liver abscess
  - Recurrent pancreatitis
- Genitourinary tract
  - Hydronephrosis
  - Urinary tract infection
  - Urolithiasis
  - Dysmenorrhea
  - Pelvic inflammatory disease
  - Mittelschmerz
- Miscellaneous
  - Malignancies
  - Sickle cell crisis
  - Lead poisoning
  - Vasculitis (especially Henoch-Schönlein purpura)
  - Angioedema
  - Acute intermittent porphyria
  - Familial Mediterranean fever

LABORATORY EVALUATION

- Laboratory and diagnostic studies performed without medical indications may not be helpful and may hinder therapeutic suggestions in FAP.
- Dysfunctional and psychogenic causes account for most diagnoses of FAP with nonfunctional causes identified in only 5%–8%.
  - When these causes are suggested by history and physical examination, urinalysis could suffice as initial laboratory study.
- Testing is indicated when alarm signals or abnormal physical findings suggest nonfunctional disorder.
- Suggested screening tests for all patients
  - Complete blood cell count with differential
  - Erythrocyte sedimentation rate
  - Comprehensive metabolic panel
  - Stool Hemoccult
- Suggested screening tests for patients with diarrhea
  - Stool culture
  - Stool ova and parasite
  - *Giardia* enzyme-linked immunosorbent assay
  - *Clostridium difficile* toxin or polymerase chain reaction
  - Celiac panel
  - Lactose or fructose breath test
- In suspected pancreatitis
  - Amylase
  - Lipase
- In patients with dyspepsia
  - *Helicobacter pylori* stool antigen testing

IMAGING

- Choice of imaging tests should be guided by differential diagnosis generated by history and findings on physical examination.
- Ultrasound of abdomen or pelvis is not useful in the absence of alarm symptoms but is useful with atypical symptoms such as
  - Jaundice
  - Urinary symptoms
  - Back or flank pain
  - Vomiting
  - Abnormal physical findings
- Ultrasound is a safe way to assess the need for urgent surgical intervention in suspected problems such as intussusception, ovarian torsion, and kidney abscess.
- Upper GI series should be considered in recurrent vomiting to define potential anatomic abnormalities such as gastric outlet disorder or malrotation.

TREATMENT APPROACH

- Treatment for acute abdominal pain resulting from a nonfunctional process should follow guidelines for that condition.
- FAP should be approached as a biopsychosocial phenomenon.
  - Response can be subjective.
  - Treatment may be a combination of psychotherapy, pharmacology, diet, and alternative medicine.
  - Educating the child and parent about cause of pain and treatment plan improve adherence and affect outcome.

SPECIFIC TREATMENT

Acute Abdominal Pain

- Acute abdominal pain falls into 3 broad categories.
  1. Conditions requiring immediate surgical intervention
     - Closed loop intestinal obstruction
     - Volvulus (gastric, midgut, sigmoid)
     - Incarcerated hernia (inguinal, internal, external)
     - High-grade bowel obstruction
     - Non-reducible intussusception
     - Malrotation with Ladd bands
     - Ovarian torsion
     - Testicular torsion
     - Acute appendicitis
     - Perforated viscus with diffuse peritonitis or toxicity
     - Ruptured tumor
     - Ectopic pregnancy
  2. Conditions that may be managed medically at first but may require surgery
     - Partial small bowel obstruction
     - Postsurgical adhesions
     - Crohn disease
     - Lymphoma
     - Appendiceal abscess
     - Abdominal abscess
     - Cholecystitis
     - Gallbladder hydrops
     - Pancreatitis
     - Pancreatic pseudocyst
     - Toxic megacolon or typhlitis
  3. Conditions that can be managed medically
     - Upper respiratory infection, pharyngitis
     - Viral gastroenteritis (mesenteric adenitis)
     - Pneumonia
     - Partial bowel obstruction
     - Paralytic ileus
     - Fecal impaction
     - Meconium ileus equivalent in cystic fibrosis
     - Bacterial enterocolitis
     - Acute gastritis or peptic ulcer
     - Acute constipation
     - Flare of FAP
     - Acute hepatitis
     - Perihepatitis (Fitz-Hugh–Curtis syndrome)
     - Inflammatory bowel disease (Crohn disease and ulcerative colitis)
     - Henoch-Schönlein purpura
     - Hemolytic uremic syndrome
     - Collagen vascular disease
     - Hereditary angioedema
     - Pyelonephritis
     - Renal calculi
     - Pelvic inflammatory disease
     - Sickle cell crisis
     - Diabetic ketoacidosis
     - Dysmenorrhea
     - Mittelschmerz
     - Poisoning
     - Porphyria
     - Intestinal gas pain

Functional Abdominal Pain

- May be explained as alteration in brain-gut axis
  - No specific test to confirm diagnosis, but inciting events may trigger pain.
  - Goal of therapy is to have child resume regular lifestyle.
- Psychosocial treatment
  - Cognitive-behavioral therapy combining operant elements and stress management.
    - Results in short-term improvement with more than half of patients experiencing freedom from pain
  - Anxiety is an associated comorbidity with FAP and psychological therapy may be a strategy.
  - Alternative medicine techniques are becoming more common.
    - Mind-body techniques such as breathing exercises, guided imagery, progressive muscle relaxation, biofeedback, hypnosis, and music therapy
- Medical management
  - Several drugs have been used to treat recurrent abdominal pain in childhood, including
    - Famotidine.
    - Pizotifen.
    - Peppermint oil in the form of a pH-dependent, enteric-coated capsule.
    - Citalopram, a selective serotonin reuptake inhibitor, has been used in FAP with improvement of abdominal pain, anxiety, depression, and functional impairment.
    - Amitriptyline has been shown to reduce pain, depressive symptoms, somatization in children with FAP, and irritable bowel syndrome.
  - Other medications (eg, anticholinergics, antiemetics, other antidepressants, simethicone) are commonly used but insufficiently studied.
  - Probiotics have been used in ulcerative colitis and antibiotic-associated diarrhea, but there is little evidence to support use in FAP.

- Dietary interventions are understood by parents and children and suggesting these may empower the family.
  - High-fiber diet (primarily in constipated children, to substitute for nutrient-poor, high-fat, high-calorie diet)
  - Avoidance of lactose
  - Oligoantigenic diet
  - Low-oxalate diet (for abdominal migraine)

WHEN TO REFER

- Involuntary weight loss
- Deceleration of linear growth
- GI blood loss
- Significant vomiting
- Chronic severe diarrhea
- Persistent right upper or right lower quadrant pain
- Unexplained fever
- Family history of inflammatory bowel disease
- Extraintestinal symptoms
- History of psychiatric disorder
- Abnormal test results
- Anemia or low mean corpuscular volume
- Peripheral eosinophilia
- Increased erythrocyte sedimentation rate
- Increased transaminases
- Increased blood urea nitrogen or creatinine
- Hypoalbuminemia
- Low complement-4 protein

WHEN TO ADMIT

- Hospitalization is required in the following circumstances:
  - Surgical or medical emergency as determined by diagnostic or therapeutic intervention
  - Inability to tolerate enteral nutrition
  - Inability to maintain hydration status
  - Diagnosis that requires observation to monitor clinical status
- Hospitalization is seldom indicated in FAP, and some studies indicate it may reinforce pain behavior and lead to worse outcome.

PROGNOSIS

- Depends on the cause of the acute or recurrent abdominal pain

Acne

DEFINITION

- Acne is a disease of the pilosebaceous unit in which sebaceous glands become enlarged and increase their production of sebum.
- Increased sebaceous gland activity is necessary for acne to develop.

SIGNS AND SYMPTOMS

- Non-inflamed open and closed comedones.
  - Obstruction of pilosebaceous canal causes
    - Open comedones (blackheads)
    - Closed comedones (whiteheads)
  - Closed comedones (whiteheads) appear as dome-shaped, flesh-colored papules that are often overlooked.
  - Acne in prepubertal children is predominantly noninflammatory and easily overlooked.
- Inflammatory papules and pustules.
  - Rare in young children and suggest a possible hyper-androgenic condition, including
    - Congenital adrenal hyperplasia
    - Rare androgen-secreting tumor
  - Examine for precocious puberty in both sexes and virilization in girls.
- Cystic acne in severe cases.
  - Nodules >5 mm in diameter
  - True cysts (compressible nodules under normal-appearing skin)
  - Can result in permanent acne scars
- Lesions appear most frequently on the face.
  - They also often appear on the chest and back.
  - Conchal bowls of the ears may be affected.
  - Lower portions of the trunk, buttocks, and thighs are involved less frequently.
  - Distal extremities are always spared.

DIFFERENTIAL DIAGNOSIS

Flat Warts

- Small, flesh-colored.
- Sharp, right-angled edge and finely roughened surface.
- Variable in size.
- Closed comedones are smooth, dome-shaped, and uniformly small.

Milia

- Small epidermal inclusion cysts
- Also confused with inflammatory pustules, especially in neonates with neonatal acne

Adenoma Sebaceum

- Pink papules that are occasionally confused with acne lesions.
- Lesions are actually angiofibromas.
  - A dermal manifestation of tuberous sclerosis
  - Can also be seen in multiple endocrine neoplasia
- Adenoma sebaceum lesions should be suspected if they are
  - Clustered primarily in the center of the face
  - Persistent
  - Resistant to acne therapy

Rosacea

- An acneiform eruption that can be distinguished from acne by
  - Background blush of erythema and telangiectasia
  - Absence of comedones
- Most often found in middle-aged adults.

Steroid Acne

- Can be induced by systemic or topical steroids
- Lacking in comedones
- Involutes slowly and spontaneously after discontinuation of steroids
- Acne from systemic steroids usually is
  - Made up of numerous small, uniform-sized papules and pustules
  - Found on the upper trunk
  - Lacking in comedones

Gram-negative Folliculitis

- Caused by gram-negative organisms in patients being treated for acne with systemic antibiotics
- Should be suspected in patients whose disease flares up during therapy
  - Especially when flare-up produces numerous pustules

Acne Conglobata

- Unusually severe acne variant caused by
  - Sudden deterioration of existing active acne
  - Recurrence of acne that has been quiet for many years
  - Most common in 18- to 30-year-old men
    - Lesions consist of
      - Comedones
      - Cysts with foul-smelling seropurulent material
      - Burrowing and interconnecting abscesses, leaving irregular and disfiguring scars

A

- Associated with systemic diseases, such as
  - Hidradenitis suppurativa
  - Pyoderma gangrenosum
  - Renal amyloidosis
  - Musculoskeletal syndrome
- The mainstay of treatment is isotretinoin.

Acne Fulminans

- A rare and severe form of acne.
  - Usually occurs in men
  - Characterized by
    - Sudden onset of painful acne nodules.
    - Rarely by ulcerative lesions.
    - Systemic symptoms include fever, leukocytosis, polyarthritis, splenomegaly, erythema nodosum, and lytic bone lesions in long bones, clavicle, and sternum.
- Treatment involves a combination of systemic corticosteroids initially, followed by isotretinoin.
- Prognosis is good, although residual scarring and disfigurement may persist.

DIAGNOSTIC APPROACH

- Diagnosis is rarely difficult.
- Comedonal lesions may require closer inspection to avoid confusion with
  - Warts
  - Milia
  - Adenoma sebaceum
  - Acne variants

LABORATORY FINDINGS

- In cases of possible hyper-androgenic condition, screening blood studies should include serum levels of
  - Testosterone
  - Androstenedione
  - Dehydroepiandrosterone sulfate
  - 17-hydroxyprogesterone
  - Follicle-stimulating hormone
  - Luteinizing hormone
- In possible gram-negative folliculitis
  - Bacterial culture with antibiotic sensitivity studies

TREATMENT APPROACH

- Acne is important to the patient seeking help and should be managed seriously.
  - Some young people appear to be more affected psychologically than others, but no one is comfortable with acne.
- Five methods of treatment have proved effective.
  - Topical comedolytic agents
  - Topical and systemic antibiotics
  - Systemic retinoids
  - Systemic hormonal therapy
  - Combination of comedolytics and antibiotics (most traditional and effective treatment regimen)

SPECIFIC TREATMENTS

Comedolytics

- Retinoids
  - Mainstay of acne treatment.
  - In most cases, topical retinoids (alone or in combination) should be used as first-line therapy for mild to moderate inflammatory acne in addition to comedonal acne.
  - Topical retinoids help disimpact the keratinous plug in the follicular canal.
  - Topical comedolytics are available in a variety of preparations; the preparation strength reflects its irritancy and probably also its efficacy.
  - Available in combinations to aid compliance, such as tretinoin combined with clindamycin and adapalene with benzoyl peroxide.
    - Tretinoin
      - Preparation strength depends on drug concentration and nature of the vehicle in which it is contained.
      - Cream in 0.025% (mildest), 0.05% (mild), 0.1% (moderate).
      - Gel in 0.01% (mild), 0.025% (moderate), 0.05% (strongest).
      - Solution in 0.05% (strongest).
    - Adapalene
    - Tazarotene
    - Benzoyl peroxide
    - Salicylic acid
    - Sodium sulfacetamide
  - Most helpful in treating superficial acne lesions, including comedones and superficial papules and pustules.
  - Reduces inflammatory lesions and enhances penetration of other medications.
  - Preferred agent for maintenance therapy.
- In combination with another topical agent
  - Apply the retinoid at bedtime and the other agent each morning.
    - If the other agent is a wash, both agents can be applied in the morning or the evening, which may facilitate compliance.

- Adapalene.
  - Gel in 0.1% and 0.3% concentration
  - Cream in 0.1%
- Tazarotene.
  - Gel and cream are each available in concentrations of 0.05% and 0.1%.
- Benzoyl peroxide.
  - Gel in concentrations of 2.5%, 5%, and 10%
- Salicylic acid.
  - Large variety of preparations and concentrations
- Sodium sulfacetamide.
  - Lotion in 10% concentration
- Mildest preparations are initially prescribed; potency is increased if necessary.

■ Side effects
- Skin irritation is the most common.
  - Can be associated with overuse.
  - Counsel patients to use no more than a pea-sized amount of medication for the entire face.
  - Adjunctive use of emollients can mitigate this effect.
- ~1% of patients develop true allergic contact dermatitis to benzoyl peroxide.
  - Requires permanent discontinuation of this agent
- Benzoyl peroxide can bleach clothing and linens.
- Topical retinoids may make the skin more susceptible to the effects of sunlight.
  - Patients should avoid excessive exposure to the sun and use oil-free sunscreens.

Antibiotics

■ Indicated for inflammatory acne lesions

■ Topical agents
- Erythromycin
- Clindamycin
  - Use as monotherapy is not recommended for more than a few weeks because of slow onset of action and predictable emergence of antibiotic-resistant bacterial organisms.
- Combinations of benzoyl peroxide and erythromycin or clindamycin, or tretinoin and clindamycin, are often prescribed before oral antibiotics.
  - Benzamycin gel (5% benzoyl peroxide and 3% erythromycin) twice daily
  - BenzaClin gel (5% benzoyl peroxide and 1% clindamycin phosphate) twice daily
  - Acanya gel (2.5% benzoyl peroxide and 1.2% clindamycin) once daily
  - Veltin or Ziana gels (0.025% tretinoin and 1.2% clindamycin) nightly

■ Systemic antibiotics are warranted if acne lesions are inflammatory and either are extensive enough to make topical therapy impractical (ie, involving the neck, shoulders, and upper trunk) or are unresponsive to a topical regimen
- Tetracycline class is preferred in patients >8 years.
  - Second-generation tetracyclines doxycycline and minocycline are preferred.
    - Flexible dosing options (twice daily, or once daily if using extended-release formulations Doryx [doxycycline], Oracea [doxycycline], or Solodyn [minocycline])
    - Increased lipophilicity and follicle penetration
    - High efficacy against *Propionibacterium acnes*
- Erythromycin may be used as an alternative if the patient does not respond to tetracycline.
  - Highest rate of *P acnes* resistance among oral antibiotics prescribed for acne
- Doxycycline and minocycline may also be substituted.
  - Doxycycline is more likely to cause photosensitivity.
  - Minocycline
    - Very expensive
    - Sometimes associated with drug hypersensitivity syndrome, Stevens-Johnson syndrome, and lupus-like syndrome

■ Resistance to *P acnes* may affect ≤25% of patients taking antibiotics.
- Preventive measures should be taken.
  - Limiting the use of oral antibiotics to shorter periods
  - Combining topical comedolytics (especially topical retinoids) with topical antibiotics
  - Avoiding the use of oral antibiotics as maintenance therapy

Systemic Retinoids

■ Isotretinoin
- Reduces follicular keratinization, sebum production, and intrafollicular bacterial counts, resulting in dramatic improvement.
- Therapeutic effect usually takes several months and often persists long after therapy is discontinued.

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- Historically, 6-month courses have been used, but recently, some practitioners focus on total dose given rather than duration.
  - Target is 100 to 150 mg/kg total dose.
- Side effects are common.
  - Almost all patients experience mucocutaneous reactions (cheilitis, conjunctivitis, dry mucous membranes of the mouth and nose).
  - Extra-cutaneous complications, including
    - Plasma lipid elevation
    - Asymptomatic vertebral hyperostoses
    - Pseudotumor cerebri (rarely)
    - Inflammatory bowel disease (IBD); relationship with isotretinoin confounded by
      - Overlap between the highest age of IBD occurrence and the age when severe acne occurs and isotretinoin is used
      - Extended history of antibiotic use in most patients receiving isotretinoin
      - Possible link between IBD and inflammatory acne itself
    - Mood disorders
      - Almost all evidence for association is anecdotal.
      - Larger, well-designed epidemiologic studies have not supported a cause-and-effect relationship between isotretinoin and depression.
      - Acne severity is a proven predictor of mental health issues and suicidal ideation.
      - Although patients taking isotretinoin should be carefully observed for mood changes, evidence is reassuring.
  - Female patients must exercise strict birth control while taking this drug.
    - Exposure to isotretinoin in pregnancy has been associated with a 25-fold increased risk of major fetal malformations.
      - The US Food and Drug Administration (FDA) requires that all patients being prescribed isotretinoin be enrolled in a national registry.
- Isotretinoin is recommended only for
  - Patients with severe cystic and/or scarring acne
  - A minority of patients who have severe non-cystic acne and have not responded to topical comedolytics and oral antibiotics

Hormonal Therapy

- An excellent option for women with moderate to severe acne if
  - Oral contraception is desired.
  - An alternative to repeated courses of isotretinoin is preferred.
  - Certain endocrine disorders are present.
    - In absence of endocrine disorders, wait until 1 year after menstruation onset to allow the development of bone mineral density before initiating oral contraceptives.
- All combination contraceptives reduce free testosterone and have a positive effect on acne.
  - No single preparation is demonstrably superior.
- Avoid contraceptives containing only progestins because intrinsic androgenic activity may aggravate acne.
- Only the progestins norgestimate, desogestrel, and drospirenone have no or low risk for increasing testosterone receptor activity and can be used in combination formulations.
- The FDA is reviewing the relationship between oral contraceptive use and thromboembolism.
- Obtain a history of tobacco use and family history of thrombotic events before prescribing oral contraceptives.
- Spironolactone
  - Aldosterone antagonist that reduces receptor binding by testosterone and dihydrotestosterone in sebaceous glands and reduces free testosterone.
  - Efficacy may be more quickly apparent than when oral contraceptives are used, often in 2–3 months instead of 3–4 months.
  - Dose range: 25–200 mg daily.
  - Monitor blood pressure and serum potassium levels; at higher doses, it can lower blood pressure and raise potassium levels.

Patient Compliance

- Patient compliance is the single most important aspect of successful acne treatment.
- To maximize compliance
  - Take time at the initial visit to explain use, anticipated effects, and side effects of each medication.
    - Printed instructions are good reinforcement.
  - Depending on the situation, medications can be taken once or twice daily.
    - Link to an established daily routine, such as brushing teeth.

- Emphasize the concept that the treatment will take time to be effective.
- The most common patient questions, often unasked, pertain to diet, cleanliness, cosmetics, and picking at the lesions.

Diet

- Diet has long been dismissed as a factor in the development of acne, but recent studies are changing that view.
  - High-glycemic-load diets
    - — May exacerbate acne.
    - — More studies are needed before carbohydrate restriction can be strongly recommended.
    - — Recommending a low-glucose-load diet as an adjunct to existing acne therapy is reasonable.
  - Dairy
    - — Association with acne is not as strong as that involving glycemic loads.
    - — May affect acne through changes in endocrine pathways.
      - Skim milk may be particularly suspect.
    - — Appropriate to advise patients that dairy products may incrementally aggravate acne.
    - — In patients who decide to avoid or significantly reduce dairy, counsel them to supplement vitamin D and calcium (**Table 1**).
  - Chocolate
    - — Recent preliminary study in adolescent boys eating 170 g (6 oz) of 100% cocoa found significant increase in the number of comedones as soon as 4 days later.
  - Other dietary components (omega-3 fatty acids, antioxidants, zinc, and fiber)
    - — Role in acne pathogenesis remains to be seen.

Cleanliness

- A primary question from parents.
  - The notion that acne is a function of poor hygiene should be dispelled.
- In general, cleaning agents for acne are unnecessary.
  - Most irritate the skin, compounding irritation caused by topical comedolytics.
- A mild soap-free cleanser is often suggested.

Cosmetics

- Preferable to avoid use.
- If used, they should be water based and applied sparingly.
- If eruption is prominent and negatively affecting the patient's self-image, corrective camouflage is an option.

Picking

- Much skin damage in acne patients is self-inflicted.
- Picking, probing, and squeezing can cause tissue damage and produce scars.
- For some, picking may become so obsessive that excoriations are the only lesions seen.

WHEN TO REFER

- Patients unresponsive to oral antibiotics and topical comedolytics.
- Patients with cystic or scarring acne.
- Young girls with acne or girls with acne and irregular menses.
- Patients with acne fulminans.
  - Abrupt onset of cystic acne, fever, arthralgias
- Consider referral to a pediatric endocrinologist if there is reason to suspect a hyper-androgenic basis.

FOLLOW-UP

- The first scheduled return visit should be 2–3 months after start of therapy.
  - Improvement usually occurs within this period.
  - Regimen can be adjusted as necessary, eg, comedolytics and antibiotics can be increased or reduced depending on response.
- Continued improvement is to be expected with continuation of therapy.
  - For many, the dose of systemic antibiotics can be reduced gradually and eliminated after 6–12 months.
  - Most patients require prolonged maintenance therapy (often over years) with topical agents.
  - Some require continued topical antibiotic therapy.

COMPLICATIONS

- The major complications are psychosocial ramifications.
  - May be compounded and perpetuated by permanent scars
- Scars are easier to prevent than to treat.
  - Emphasis is on early, aggressive medical therapy.
- Established scars are difficult to treat.
  - Acne scars are best treated when inflammatory lesions are quiescent.

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- Many patients have been disappointed with the results of dermabrasion.
  - Patients treated with isotretinoin should wait for at least 1 year before having dermabrasion.
- Bovine collagen injections have produced short-term improvement.
  - Repeated injections are often necessary.
  - Long-term results are not yet known.
- Laser resurfacing by experienced operators has shown promising results.

PROGNOSIS

- With proper treatment, the prognosis for acne is good to excellent.
- Patients should understand that most therapy controls rather than cures acne.
- Cystic acne has been the most difficult to treat, but with isotretinoin, there is potential for prolonged remission.
  - Because of serious side effects, use is usually reserved for patients with severe cystic or scarring acne unresponsive to standard treatment.

Table 1. Dietary Reference Intakes for Calcium and Vitamin D

Life-Stage Group (age and gender)	Calcium		Vitamin D	
	RDA (mg/d)	Upper limit (mg/d)	RDA (IU/d)	Upper limit (IU/d)
0–6 mo (M + F)	200	1,000	400	1,000
6–12 mo (M + F)	260	1,500	400	1,500
1–3 y (M + F)	700	2,500	600	2,500
4–8 y (M + F)	1,000	2,500	600	3,000
9–13 y (M + F)	1,300	3,000	600	4,000
14–18 y (M + F)	1,300	3,000	600	4,000

Abbreviation: RDA, recommended dietary allowance; intake that covers needs of 97.5% of the healthy normal population.

Reflects adequate intake (AI) reference value rather than RDA. RDAs have not been established for infants because of insufficient data.

Calcium and vitamin D RDAs are the same for pregnant or lactating females in these age groups.

Reprinted with permission from *2011 Dietary Reference Intakes for Calcium and Vitamin D,* by the National Academy of Sciences. Courtesy of the National Academies Press, Washington, DC.

Adjustment Disorder

DEFINITION

- Adjustment disorder (AD) is a maladaptive response to a stressor, resulting in clinically significant emotional or behavioral symptoms not meeting criteria for a more specific disorder.
- Clinical significance is determined by marked distress in excess of that expected or by impairment in social or occupational (academic) functioning.
- No minimum duration of symptoms is necessary for the diagnosis; symptoms must occur within 3 months of the onset of the stressor.
- Symptoms cannot persist for more than 6 months after termination of the stressor, with the exception of chronic cases in which the stressor persists.

SIGNS AND SYMPTOMS

- Distress and impairment in functioning manifested by decreased performance in school, work, or relationships.
- Children and adolescents are more likely than adults to present with behavioral disturbance than with depressed mood.
- Symptom presentation also depends on the subtype.
  - Young children with a depressed mood
    - Sadness
    - Tearfulness
    - Change in appetite and sleeping pattern
    - Loss of interest in play
  - Older children/teens
    - Irritability
    - Loss of energy
    - Fatigue
    - Feeling slowed down or burned out
    - Excessive feelings of guilt
    - Inability to concentrate
    - Indecisiveness
    - Hopelessness
    - Thoughts of suicide
    - Substance use
    - Somatic complaints
  - Anxiety subtype of AD
    - Symptoms of nervousness, worry, jitteriness, or fear of separation
    - Disturbances in conduct and emotions

DIFFERENTIAL DIAGNOSIS

- Determine if the child/teen meets criteria for another disorder.
  - Major depressive disorder
  - Dysthymia
  - Generalized anxiety disorder
  - Acute stress/posttraumatic stress disorder (PTSD)
  - Somatization disorder
  - Oppositional defiant disorder
  - Conduct disorder
  - Substance use disorder
- Always consider trauma in the differential diagnosis.
  - Unlike AD, in PTSD, the stressor is extreme and involves actual or threatened death or serious injury accompanied by a specific constellation of symptoms.
  - A child may be suffering from the effects of early toxic stress (see Signs and Symptoms section).
    - Such a history should alert the physician to the possibility of complex developmental trauma and its attendant psychological and behavioral sequelae.
- A pattern of frequent, recurrent "adjustment reactions" can point to the presence of a more pervasive psychiatric disorder.

DIAGNOSTIC APPROACH

- Identification of AD can be challenging.
  - Assessment of what constitutes a stressful event and a maladaptive response is subjective.
- The pediatrician is often in a unique position to make this determination.
  - Mental health professionals often first come into contact with the child in the midst of a crisis, but the child's pediatrician often has worked with child and family over a long period and has a working sense of his or her developmental level, coping skills, and strengths.
- Diagnostic tools
  - Pediatric Symptom Checklist (PSC-17)
    - General psychosocial screen to identify symptoms in the domains of attention, internalizing, and externalizing
  - Patient Health Questionnaire (PHQ-9M)
    - Modified screen for depression in teens
    - Maps onto the *Diagnostic and Statistical Manual of Mental Disorders* criteria for depression
    - Modified to include questions on suicidality
  - CRAFFT (**c**ar, **r**elax, **a**lone, **f**orget, **f**riends, **t**rouble)
    - Short validated tool that asks teens about
      - Riding in a car with someone who is "high" with alcohol or drugs
      - Whether the teen uses alcohol or drugs to relax

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  - Whether the teen uses these alone
  - Whether the teen has forgotten events after using
  - Whether family and friends are worried about his or her use
  - Whether he or she has gotten in trouble as a result of use
- Scoring can be used to assess probability of use disorder or dependence.
- Also remember to inquire about tobacco use.

- Risk assessment for suicide: the SAD PERSONS mnemonic plus family history
  - **S**ex (Females attempt more often, but males are more likely to complete.)
  - **A**ge >16 years
  - **D**epression (and comorbid conduct/impulsive aggression/anxiety)
  - **P**revious attempts
  - **E**thanol use disorder (or other substance)
  - **R**ational thinking lost (eg, psychotic/intoxicated)
  - **S**ocial supports lacking
  - **O**rganized plan present (highly lethal and unusual method with wish to die/concealment)
  - **N**o significant other available (eg, a close friend)
  - **S**ickness (stressors)
  - First-degree relative who has completed a suicide

CLASSIFICATION

- The subtypes of AD are based on the nature of the disturbance.
  - With depressed mood
  - With anxiety
  - With mixed anxiety and depressed mood
  - With disturbance of conduct
  - With mixed disturbance of emotions and conduct
  - Unspecified

TREATMENT APPROACH

- Treatment of AD calls for a broad, systemic view of the patient's problems.
- Goals of treatment
  - To reduce emotional and behavioral distress
  - To improve functioning
- Use "common factors" techniques to build a therapeutic alliance with the child and family (**Box 1**).
  - Trans-diagnostic approach to effective practice elements rather than a specific protocol for a certain diagnosis.
  - Improves outcomes across a range of diagnoses and could be useful in AD, given the subsyndromal, potentially evolving nature of this diagnosis.
  - Common factors can provide well-defined and manageable tools to further the discussion on mental health and engage patients in addressing these problems.
- Individual level
  - Foster resilience—identifying and bolstering coping skills and problem-solving around issues related to stressor.
  - Parents can be important partners, particularly for younger patients, by encouraging healthy means of coping.
  - Educate child and parents about effects of stress and the role of coping.
  - Identify other supports (eg, teachers, counselors, coaches) for additional help.
  - Discuss a safety plan in case symptoms worsen or danger (suicidal or homicidal ideation) arises.
- Environmental approach
  - Environment can include parents, family, school, peers, or the larger community.
    - All can play a role in predisposing, precipitating, or perpetuating the presenting problem.
    - For example, if bullying is leading to maladjustment, contacting the school and discussing intervention strategies with the staff can improve the situation.
  - Many other forms of stressors (eg, contentious parental divorce) do not lend themselves to similar swift intervention but require attention, as they are likely to perpetuate symptoms.
- Those with a history of several toxic stressors presenting with a maladaptive response to a new problem will likely require greater intervention than those with a stable caregiver relationship and unremarkable psychosocial history.

SPECIFIC TREATMENTS

- Treatment of choice is psychotherapy.
  - Given the prominent psychosocial determinants of AD, nonpharmacologic interventions are the treatments of choice.
- No empirically validated treatments exist specifically for AD, but there are many psychotherapeutic treatments for full-blown syndromes such as depression, generalized anxiety, disruptive behavior disorders, and trauma.

Box 1. HELP Build a Therapeutic Alliance

H = Hope

Increase the family's hopefulness by describing your realistic expectations for improvement and reinforcing the strengths and assets you see in the child and family.

E = Empathy

Communicate empathy by listening attentively.

L^2 = Language, Loyalty

Use the child's or family's own language to reflect your understanding of the problem as they see it and to give the child and family an opportunity to correct any misperceptions.

Communicate loyalty to the family by expressing your support and your commitment to help.

P^3 = Permission, Partnership, Plan

Ask the family's permission for you to ask more in-depth questions or make suggestions for further evaluation or management.

Partner with the child and family to identify any barriers or resistance to addressing the problem, find strategies to bypass or overcome barriers, and find agreement on achievable steps aligned with the family's motivation.

Establish a plan (or incremental first step) through which the child and family will take some action(s), work toward greater readiness to take action, or monitor the problem, then follow up with you, based on the child and family's preferences and sense of urgency. (The plan might include, for example, gathering information from other sources such as the child's school, making lifestyle changes, applying parenting strategies or self-management techniques, reviewing educational resources about the problem or condition, initiating specific treatment, seeking referral for further assessment or treatment, or returning for further family discussion.)

From American Academy of Pediatrics. *Addressing Mental Health Concerns in Primary Care: A Clinician's Toolkit* [CD-ROM]. Elk Grove Village, IL: American Academy of Pediatrics; 2010.

- In theory, these can be applied to prominent symptoms of AD.
  - Cognitive behavioral therapy (CBT) and interpersonal therapy for depression
  - CBT for anxiety
  - Trauma-focused CBT
- Treatment is delivered in many individual and group formats, but little is known about the optimal structure, frequency, and intensity for AD.
- Consider family therapy in cases of severe and persistent distress.
- Medication does not have an established evidence base in the treatment of AD.
  - There is no US Food and Drug Administration–approved medication for AD.
  - Benzodiazepines
    - No proven efficacy in controlled trials in childhood anxiety.
    - Have been used clinically with selective serotonin reuptake inhibitors (SSRIs) as adjunctive short-term treatment to address severe anxiety symptoms and facilitate CBT.
    - Role in AD has not been studied.
    - Contraindicated with substance use.
    - Side effects include sedation, disinhibition, cognitive impairment, and difficulty with discontinuation.
  - SSRIs
    - In adults, in cases of prolonged stress, such as chronic illness and medical hospitalization, SSRIs have been used to help bolster resilience and recovery.
    - No reports or similar studies in children with AD.

WHEN TO ADMIT

- Hospitalization of a child or teen with AD is unlikely to be necessary in the absence of severe impairment and active suicidal thoughts or plan.

WHEN TO REFER

- Consider referring to mental health services if problems with coping persist or worsen.

FOLLOW-UP

- Ongoing follow-up with primary care or mental health specialty care is indicated for monitoring of symptom resolution and return to normal social functioning.

PROGNOSIS

- For most, prognosis is good.
- More children and teens, as compared with adults, experience a poor outcome with continued disturbance and progression to specific disorders.

PREVENTION

- Further research is needed to determine if AD is
  - A subthreshold presentation of PTSD
  - A variant of a less severe affective, anxiety, or behavioral disorder
  - An entirely different disorder independent of any of these conditions

Allergic Rhinitis

DEFINITION

- Atopic disease caused by exposure to allergens and characterized by nasal congestion, sneezing, rhinorrhea, and pruritus
  - Seasonal variation (hay fever)
  - Year-round (perennial) form
- May exist alone or in combination with asthma or atopic dermatitis

SIGNS AND SYMPTOMS

- Clinical presentation varies greatly by location and can be affected by ambient temperature, precipitation, wind, local vegetation, and size of pollen grains.
- Characterized clinically by a combination of nasal congestion, sneezing, rhinorrhea, and pruritus (nose, eyes, and, occasionally, palate, pharynx).
- Severity of symptoms varies depending on factors that include condition of the nose before exposure, level of specific immunoglobulin E (IgE), and intensity of antigen exposure.
- Younger children
  - Usually have perennial symptoms.
  - Significant perennial allergic rhinitis causes increased swelling in the upper airway (nose, eustachian tubes, sinus ostia).
    - Increased incidence of respiratory infection, acute otitis media, chronic serous otitis media, eustachian tube dysfunction, hearing loss, and sinusitis
- Children >4 years.
  - Pollen sensitivity is more common.
- Perennial allergic rhinitis.
  - Primary clinical effect is from inflammation and associated congestion of the upper airway.
  - Multifaceted clinical picture
    - Frequent viral upper respiratory infections (URIs)
    - Chronic serous otitis media
    - Recurrent suppurative otitis media
    - Nasal speech
    - Decreased hearing
    - Mouth breathing
    - Snoring
    - Poor sleep pattern
    - Fatigue
    - Increased risk for bronchial hyperreactivity
      - Lowers threshold for asthma from triggers such as viral URIs, cold air, dry air, exercise
  - Rhinorrhea caused by allergic triggers is typically clear and watery.
    - Can be overshadowed by purulent secretions if the child also has infectious rhinitis or sinusitis
  - Histamine release often creates intense itching in the nose and oropharynx.
    - Patients intensely rub the nose (the "allergic salute").
    - Strange clucking or throat-clearing noises to try to obtain relief.
- Physical examination in moderate to severe uncomplicated allergic rhinitis.
  - Pale, bluish, and boggy nasal mucosa with a clear serous discharge
  - Enlarged nasal turbinates, sometimes enough to obstruct the airway almost completely
  - "Allergic shiners" (dark, swollen infraorbital areas) from chronic congestion and associated obstruction of venous drainage
  - Morgan folds (extra folds below the lower eyelids)
  - Allergic crease (horizontal line across the bridge of the nose)
- More severe chronic allergic rhinitis.
  - Elongated facial growth caused by chronic mouth breathing.
    - May include orthodontic changes such as overbite and high-arched palate
  - Enlargement of tonsils and adenoids.
  - Chronic middle-ear effusion.
  - Nasal polyps can occur but are uncommon in childhood allergic rhinitis.

DIFFERENTIAL DIAGNOSIS

- Differential diagnosis of perennial allergic rhinitis
  - Viral URI
    - Acute onset of fever.
    - Purulent rhinorrhea.
    - Red, swollen nasal mucosa.
    - Sore throat.
    - Nasal cytology will show a predominance of neutrophils, but this does not preclude an allergic component as well.
  - Recurrent acute or chronic rhinosinusitis
    - Often presents as viral URI that does not resolve after 10 to 14 days.
    - Symptoms may overlap with mild allergic rhinitis, but typically patients have significant nasal obstruction and nocturnal cough.
    - Protracted acute sinusitis may lead to a chronic low-grade infectious component or induce eosinophilic nonallergic rhinosinusitis.

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- Nonallergic rhinitis with eosinophilia-myalgia syndrome (NARES)
  - Relatively rare in young children but increases in frequency in older children.
  - When NARES occurs, it may be associated with nasal polyps and asthma, much like more severe allergic rhinitis.
  - By definition, NARES patients have negative skin test results.
- Vasomotor rhinitis
  - Condition of nasal hyperreactivity to nonspecific irritant stimuli (eg, volatile organic compounds, perfumes, smoke, pollutants)
  - Chronic nasal congestion that is typically minimally improved by environmental controls or medications (unless patients have associated allergic rhinitis or rhinosinusitis)
  - Normal nasal cytology
  - Negative skin test result
  - Normal total and specific IgE tests
  - No signs of associated atopic disease (eg, asthma, atopic dermatitis)
- Nasal turbinate hypertrophy and adenoid hypertrophy
  - Important anatomic variants that cause chronic nasal obstruction.
  - Both conditions may worsen in a child with significant allergic rhinitis.
  - Children with significant nasal turbinate or adenoid hypertrophy are always congested and exhibit snoring.
  - Congestion can lead to chronic serous otitis media, decreased hearing, decreased appetite, poor sleep pattern (including sleep apnea), and orthodontic abnormalities (eg, high-arched palate, overbite, malaligned teeth).
- Less common conditions that can mimic some symptoms of allergic rhinitis
  - Nasal foreign body
  - Choanal atresia
  - Rhinitis medicamentosa
  - Cystic fibrosis
  - Ciliary dyskinesia
  - Nasopharyngeal tumors
  - Enlarged tonsils and adenoid

DIAGNOSTIC APPROACH

- Diagnosis of seasonal allergic rhinitis is generally straightforward and based on patient history, clinical presentation, and physical examination.
- Specific pollen counts can add further support for the diagnosis.
  - For local pollen counts, see the American Academy of Allergy, Asthma & Immunology Web site, www.aaaai.org.
- Nonspecific perennial symptoms pose a more difficult diagnostic challenge.

LABORATORY FINDINGS

- Nasal cytology
  - Useful adjunct if clinical diagnosis is in question.
  - The patient blows his or her nose into plastic wrap or wax paper.
    - A cotton swab may be used to obtain secretions if the patient cannot blow.
  - Secretions are spread onto a glass slide, left to dry, and treated with Hansel or Wright stain.
    - If >10% of cells seen on the smear are eosinophils, underlying eosinophilic rhinitis is suggested.
    - Strongly positive results are most likely during heavy exposure to the allergen.
    - Concurrent nasal infection may obscure the results.
    - Absence of eosinophils does not preclude allergy.
      - Sample of secretions may not have an adequate number of cells.
      - Results may be influenced by recent corticosteroid therapy.
- Leukocyte count
  - Peripheral eosinophilia is often observed.
    - >5% eosinophils on the differential leukocyte count *or*
    - >250/mcL total eosinophils
  - Not recommended as a screening test for allergic rhinitis.
- Serum IgE
  - Elevated total serum IgE level suggests atopy.
    - However, many patients who have allergic rhinitis have a normal serum IgE level.
    - Some patients with normal levels are atopic.
  - Not recommended as a screening test for allergic rhinitis.

DIAGNOSTIC PROCEDURES

- Skin tests.
- As with serology, can be useful to help direct environmental control and determine appropriate therapy.
- Skin tests are often preferred because they are less expensive and have somewhat better sensitivity.

TREATMENT APPROACH

- Treatment of allergic rhinitis is initially based on history and physical examination, which provide a framework of likely triggers and clinical severity.
  - Allergen avoidance measures
  - Pharmacotherapy
  - Occasionally, immunotherapy
- Therapy should be individualized based on
  - Patient age
  - Unique environmental factors
  - Symptom severity
  - Presence of associated medical conditions

SPECIFIC TREATMENTS

Environmental Control

- First line of therapy at all ages.
- Particular attention should be directed to the child's bedroom and other settings where substantial amounts of time are spent.
- Dust mite allergy.
  - Encase mattress, box spring, and pillows with dust mite–impervious covers.
  - Wash bedding at least weekly in hot water.
  - Minimize stuffed animals and other dust collectors in the bedroom.
- Household pets.
  - Ideally, pets should be removed if they are an important cause of symptoms.
  - This can be challenging for a family; compromise measures include
    - Keeping the pet out of the child's bedroom at all times
    - If feasible, washing the pet several times a month to help remove allergens
- Indoor molds.
  - Decrease moisture levels.
    - More effective exhaust fans in the bedroom and kitchen, installing double-pane windows, or using a dehumidifier
- Pollens.
  - Close windows and use an air conditioner.
  - With forced-air heating and cooling, it can be helpful to install a filter that can remove all indoor allergens (<5 mcm) and a humidifier or dehumidifier to maintain relative humidity in the 40%–50% range.
    - Humidity in this middle range discourages dust mites, cockroaches, and mold growth but avoids the irritant effect of dry air.

Pharmacotherapy

- Primary pharmacotherapy
  - Antihistamines (oral and nasal)
  - Leukotriene receptor antagonists
  - Nasal corticosteroids
- Adjunctive medications
  - Decongestants
  - Nasal cromolyn
  - Nasal ipratropium
  - Oral corticosteroids

Antihistamines (Oral and Nasal)

- First-line pharmacologic treatment.
- Block histamine (H_1) receptors on mast cells, thus preventing rhinorrhea, sneezing, and itching caused by histamine.
- Recently developed antihistamines are typically effective with relatively low risk for side effects such as sedation.
  - Fexofenadine
  - Cetirizine
  - Levocetirizine
  - Loratadine
  - Desloratadine
- First-generation antihistamines, such as chlorpheniramine, diphenhydramine, hydroxyzine, and triprolidine, are effective, but their utility is often limited by their sedative side-effect profile.
- Nasal antihistamines, such as azelastine and olopatadine, represent an alternative approach to oral antihistamines.
  - Some risk for sedation because the medication is absorbed from the nose

Leukotriene Receptor Antagonist

- Montelukast
  - Approved for treatment of seasonal and perennial allergic rhinitis
  - Generally well tolerated
  - Can be used as monotherapy or combined with antihistamines

- Can be particularly useful in children who have concurrent asthma or who will not comply with the use of nasal sprays

Nasal Corticosteroids

- The most effective monotherapy for allergic rhinitis.
- Some formulations have been approved for use in children ≥2 years.
  - Available formulations
    - Beclomethasone
    - Budesonide
    - Ciclesonide
    - Flunisolide
    - Fluticasone propionate
    - Fluticasone furoate
    - Mometasone furoate
    - Triamcinolone
- Growth suppression is a theoretical risk with nasal steroids, so the lowest effective dose should be used.
- Fortunately, several of the newer formulations have reduced bioavailability and are typically well tolerated.

Decongestants

- May be useful in the short term to help reverse the effects of acute congestion
- Oral formulations
  - Significant potential for causing irritability, hyperactivity, or sleep disturbances
- Nasal formulations
  - Use should also be limited because prolonged therapy can induce rebound congestion (rhinitis medicamentosa).
- Nasal cromolyn sodium
  - Well tolerated, but its use is limited because optimal efficacy requires use 4–6 times a day.
- Nasal ipratropium
  - Will help control rhinorrhea but typically has little effect on other symptoms.

Oral Corticosteroids

- Can be useful in the short term to help reduce acute severe allergic inflammation.
- Provide symptom relief and reduce nasal obstruction and nasal hyperreactivity, thus creating a more favorable environment for nasal therapy.

Immunotherapy

- Consider after allergy consultation in the setting of moderate to severe allergic rhinitis that does not respond adequately to environmental controls and appropriate pharmacotherapy.
- Typically entails a 3- to 5-year series of subcutaneous injections in a controlled setting to help induce tolerance.
- Most effective for seasonal allergic rhinitis (pollen) and dust mite allergy.
  - May also have efficacy with animal dander and molds
- Recently, sublingual allergy immunotherapy has become available to treat grass or ragweed allergy.
  - Treatment is started 12 weeks before the relevant pollen season and continued on a daily basis through the season.

WHEN TO REFER

- A board-certified allergist can help to
  - Confirm the primary diagnosis, including identification of relevant allergic triggers.
  - Exclude other subtle upper and lower airway nonallergic diseases.
  - Fine-tune environmental control and pharmacotherapy.
- Consider referral for
  - Poor clinical course despite aggressive environmental controls and appropriate frontline medications
    - Persistent perennial symptoms
    - Poorly controlled seasonal rhinitis symptoms
    - Suspected complications (eg, chronic sinusitis)
    - Recurrent otitis media, recurrent sinusitis, or worsening persistent or intermittent asthma
    - Consideration of allergen-specific immunotherapy

PROGNOSIS

- Prognosis is often related to environmental triggers, unique genetic factors, and willingness to comply with suggested treatment.
- Perennial allergy effects tend to lessen over time.
  - Environmental controls have an increased effect on indoor allergen exposure.
  - Allergens tend not to induce much more IgE production over time.
  - As the patient's airway gets bigger, the relative effect of these perennial factors tends to lessen.

- Seasonal allergy caused by pollens tends to worsen over time.
  - There is a predictable heavy exposure to each allergen every year that stimulates significant increases in specific IgE.

PREVENTION

- Prevention of allergy recurrence involves
  - Control of or changes in environmental factors
  - Avoidance of allergens
  - Compliance with treatment

Alopecia and Hair Shaft Anomalies

DEFINITION

- Alopecia
  - Loss of hair
- Hair shaft anomalies
  - Stubbly growth of broken hair rather than true alopecia

HISTORY

- A precise, pointed history is necessary.
- When a child loses scalp hair suddenly, a toxic event should be suspected.
  - Accidental poisoning (eg, rat poison containing thallium or coumarin).
  - In most instances, over several months, new hairs will replace lost hairs, unless the exposure to the toxic element is chronic.
- True congenital alopecia is rare.
  - May be inherited as an isolated autosomal-recessive trait or as one feature of a significant hereditary disorder
- Hairs may be thin or poorly anchored to the scalp or have a variety of shaft abnormalities.

PHYSICAL EXAMINATION

- The entire body and all its hair-bearing parts must be observed.
  - The pediatrician must not limit the examination simply to the site of hair loss.
- It is important to determine if alopecia is scarring or non-scarring.
- The texture of hair may be helpful in finding the source of difficulty.
- Appropriate diagnosis requires microscopic differentiation of the hair and its root in the anagen and telogen stages.

DIFFERENTIAL DIAGNOSIS

Congenital Alopecia

- Ectodermal dysplasia
- Skeletal defects
  - Cartilage-hair hypoplasia
  - Congenital ectodermal dysplasia
  - Orofaciodigital syndrome
- Inherited metabolic or endocrine disorders
  - Phenylketonuria
  - Homocystinuria
  - Congenital hypothyroidism
- Serious chromosomal defects
  - De Lange syndrome
  - Trisomy 13 syndrome
  - Surfeit of signs and symptoms beyond simple loss of hair

Non-scarring Alopecia With Hair Shaft Abnormalities

- Trichorrhexis nodosa
  - Common abnormality of the hair shaft characterized by
    - — Fragile, short hair with grayish-white nodules.
    - — Breakage of hair and short stubble over the scalp.
    - — White specks marking the nodes may appear after some physical and chemical injuries.
  - Usually accompanied by a history of hair straightening or repeated vigorous brushing and combing
- Monilethrix (beaded hair syndrome)
  - Scalp hairs have regularly spaced differences in their circumference, suggesting a chain of beads.
  - Fragile, short, stubble-like growth.
  - Associated problems suggestive of a more widespread ectodermal defect.
    - — Cataracts
    - — Brittle nails
    - — Faulty teeth
- Pili torti (twisted hair)
  - Fragile, short, light/"off"-colored hair appears spangled as a result of light reflection.
  - Texture is coarse and lusterless.
    - — As though straight and curly hair were competing for a place in the same strand
  - Associated with Menkes disease (kinky hair syndrome), an X-linked disease characterized by
    - — Low serum copper level
    - — Progressive cerebral degeneration with hypotonia and often with seizures
    - — Arterial degeneration
    - — Osteoporotic bones

Non-scarring Alopecia Without Hair Shaft Abnormalities

- Alopecia areata
  - Most often seen as an acute problem.
    - — Sharply demarcated, round, nearly bald patches.
    - — Inflammatory signs are not present.
  - Patches tend to be several centimeters in diameter, usually on the scalp.
    - — Possible anywhere on the body where hair is found.
    - — Loss may comprise only a few patches or a total absence of body hair (alopecia universalis), including eyebrows and eyelashes.

- Sometimes salmon-colored, as a manifestation of the presumed inflammation seen histologically around the hair follicle.
- Exclamation point hairs may appear throughout the patch.
- Hairs at the periphery of an area are plucked easily and may be particularly colorless and thin.

- Fingernails may be pitted.
  - Possible indication of a more extensive ectodermal problem
- Cause
  - Unknown, but may be related to a T-cell–mediated autoimmune process
  - Associated with acute autoimmune thyroid disease and vitiligo
  - Possible genetic susceptibility, which manifests with various environmental factors

- Androgenetic alopecia
  - Male baldness pattern.
    - Begins most often with a receding hairline and some thinning over the vertex
  - Diffuse thinning with retained frontal hair in the female.
  - Hairs from affected follicles do not epilate easily on pulling, but they are shorter and finer because of normal pubertal androgen increase.
  - Cause
    - Genetically determined
- Trichotillomania
  - Irregularly shaped areas of thinned stubble of varying lengths.
    - Large, patchy, ill-defined patterns
    - Area of hair loss is most accessible to the probing hand.
    - May simulate alopecia areata.
  - Patient may eat hair, which can accumulate in the stomach and form a trichobezoar (hair ball).
    - Abdominal pain
    - Possible acute intestinal obstruction
    - Palpable as an abdominal mass
- Cause
  - Some children have a compulsive need to pull out their hair or even eyebrows or eyelashes.
  - May sometimes (but not always) provide a major clue to an underlying psychosocial problem.
- Traumatic alopecia
  - Bizarre patterns conforming to site and method of injury
    - May be accompanied by redness and inflammation.
    - Pustular involvement of the follicles is possible.
  - Causes
- Head trauma
  - Braiding
  - Constant teasing or straightening with heat or chemicals
  - Hairstyles (eg, barrettes, ponytails, braids, cornrows) that cause constant and prolonged traction, especially along the hairline
- Telogen effluvium
  - Diffuse thinning with easy epilation from all areas of scalp.
    - Non-patterned
    - Non-scarring
  - May be difficult to distinguish from diffuse alopecia areata.
  - Hair loss may increase to ≤60%.
    - During such a period, the situation is similar to that of animals that shed seasonally.
  - Causes
    - May be related to a history of stress, including stress of childbirth in neonates
    - Prolonged fever
    - Pregnancy
    - Severe illness
- Anagen effluvium
  - Significant thinning
- Loose anagen hair syndrome
  - Hair appears sparse.
  - Hairs are quite easily and painlessly pulled from the scalp.
  - Individual hairs are not fragile.
  - Hair over the occiput often is matted and sticky.
  - Typically, the child's hair is said to be slow growing, seldom requiring cutting.
  - Causes
    - Hereditary factor may be involved.
    - Most cases are sporadic.

Potentially Scarring Alopecia Without Hair Shaft Abnormalities

- Tinea capitis and kerion
  - Presentation varies.
    - Round, minimally inflamed alopecic area with slight seborrheic scale.
    - Boggy, tender, often pustular, severely inflamed kerion.
    - Lesions tend to be more elevated than in other forms of tinea and may be characterized by black dots.

A

- Tinea capitis should be considered
  - When a child has patches of alopecia or stubbly hair growth
  - When alopecia is accompanied by local adenopathy
  - Even in the absence of crusting, scaling, redness, or other inflammatory signs
- Differential diagnosis includes
  - Seborrheic dermatitis
  - Atopic dermatitis
  - Psoriasis
- Causes
  - *Trichophyton tonsurans*
  - *Microsporum canis*
  - *Microsporum audouinii*
- Kerion
  - Delayed hypersensitivity reaction to fungus.
  - If unchecked, resultant scarring interferes with the regrowth of hair.
  - Early diagnosis and treatment are therefore helpful.

■ Lupus erythematosus
- Discoid variant
  - Discoid, well-demarcated erythematous plaques
  - Scale
  - Plugged follicles
  - Atrophy and/or thinning as a result of broken, fragile hair with acute flares (lupus hair)
  - Can be disfiguring to the scalp
  - With scarring, can cause permanent hair loss
- Systemic variant
  - Scalp may be erythematous.
  - Scarring is not characteristic.

■ Acrodermatitis enteropathica
- Abnormal zinc absorption
- Cutaneous manifestations simulating
  - Psoriasis
  - Epidermolysis bullosa
  - Pyoderma
  - Candidiasis
- Zinc deficiency can result in
  - Abdominal pain and diarrhea
  - Wispy alopecia
  - Dystrophic development of the fingernails, suggesting widespread ectodermal involvement
- Cause
  - Autosomal recessive

LABORATORY EVALUATION

■ Light microscopy
- Anagen hairs
  - Fat, healthy follicle bulbs
  - An attached, emerging long terminal hair
- Telogen hairs
  - Small bulb
  - An attached hair resulting in a club-shaped appearance

■ Light microscopic characteristics of various alopecias
- Trichorrhexis nodosa
  - Nodes along hair shaft similar to interlocking broom or brush ends
- Monilethrix
  - Variable shaft thickness gives a beaded appearance with internodal breakage.
- Pili torti
  - Irregularly spaced twists along the shaft appear flattened.
  - In cross section, a straight hair appears round and a curly hair appears oval.
  - Both configurations may be seen in a single strand; this can be an important clue to Menkes disease (kinky hair syndrome).
- Alopecia areata
  - Exclamation point hairs from periphery of patches with poorly pigmented shaft and tapered attenuated bulb
- Androgenetic alopecia
  - Increased telogen to anagen ratio
- Trichotillomania
  - Normal cuticle, shaft, and anagen bulb of varying lengths
- Traumatic alopecia
  - Normal cuticle, shaft, and anagen bulb of varying lengths
- Telogen effluvium
  - >25% of pulled hairs are telogen club hairs with no pigment.
- Anagen effluvium
  - Tapered anagen bulbs
- Loose anagen hair syndrome
  - Anagen hairs have misshapen pigmented anagen bulbs with a ruffled cuticle and no external root sheath.
- Tinea capitis and kerion
  - Potassium hydroxide preparation of broken hairs (black dot hairs) reveals clusters of chains of arthrospores around or in the hair shaft and bulb.

- Lupus erythematosus
  - Not applicable if there is scarring
  - Short, broken (frayed) anagen hairs
- Mycologic analysis
  - *T tonsurans* indicates tinea capitis.
    - In rare cases, the endothrix fungi *M canis* and *M audouinii* can invade the hair shaft and cause breakage and stubble.
    - *M canis* tends to cause much more inflammation than *M audouinii.*
    - Endothrix fungal infections, but not *T tonsurans,* can produce a greenish fluorescence under Wood light in a darkened room.

IMAGING

- Radiography
  - Congenital alopecia
    - Skeletal defects
  - Trichotillomania
    - Presence of a trichobezoar

DIAGNOSTIC PROCEDURES

- Biopsy
  - Miniaturized anagen bulbs in androgenetic alopecia
  - Fungus *T tonsurans*

TREATMENT APPROACH

- Treatment depends on the underlying cause of alopecia.
  - There may be helpful treatments.
  - The pediatrician's role may be only diagnostic and supportive.
- Strategies for the patient to hide noticeable loss of hair.
  - Suggest that the child wear a baseball cap or other concealing adornment, if appropriate.
  - A hairpiece can be designed for a child.
  - These steps serve in the interim while practitioners
    - Attempt potentially helpful treatments.
    - Wait expectantly if their role is diagnostic and supportive.
- Management if recovery of hair is questionable.
  - Work with and listen to the patient and family to
    - Achieve an emotional balance consistent with reality.
    - Adopt suitable coping mechanisms.
- Plastic surgery.
  - Expertise should be sought for consideration of hair transplants and scalp reduction (for scarred areas) when possible.

SPECIFIC TREATMENT

Trichorrhexis Nodosa

- A gentle approach results in gradual improvement.
- Eliminate any noxious exposure.

Monilethrix

- No treatment is known.
- Some degree of recovery may occur spontaneously, particularly after puberty or during pregnancy.

Alopecia Areata

- Spontaneous regrowth
  - About one-third of patients will regrow hair spontaneously in 6 months.
  - About one-third will regrow hair spontaneously ≤5 years.
  - About one-third must be treated to stimulate hair growth.
- Cortisone cream
  - Topical applications have been used with some success.
- Cortisone injection
  - Direct injection into the scalp or eyebrow hair follicles can be effective.
  - The process is painful.
  - Large areas (>50% scalp hair loss) that require infiltration present difficulty.
  - Use with caution in the older, more cooperative child.
  - The pediatrician must carefully assess the effect of the disease and the treatment on the child before selecting this procedure.
  - The patient should be referred to a dermatologist for consideration of this intervention.
- Oral corticosteroid therapy
  - Risks serious complications but is occasionally used
- Minoxidil
  - Minoxidil 5% solution twice daily can be used as an adjunct to topical corticosteroids.
  - Can be effective for small, stubborn alopecic areas.
- Latanoprost
  - A prostaglandin analog used to treat glaucoma.
  - Was noted by chance to promote the growth of eyelashes and is now commercially available.

- It and several newer agonists have had mixed results thus far in attempts to treat eyebrow and eyelash alopecia areata.
- There is no guarantee that if hair regrows in response to therapy it will persist, especially once treatment is stopped.

- Irritants
  - Used for extensive alopecia.
  - Dinitrochlorobenzene immunotherapy.
  - Tars, such as short-contact anthralin.
  - Psoralen with ultraviolet A light (PUVA therapy).
  - Use only in children and teens >12 years.
  - Should be performed only by a knowledgeable dermatologist in controlled circumstances.
- Excimer laser
  - Has shown some success even in children as young as 6 years with patchy alopecia areata
- T-cell biologics
  - Thus far have not been helpful
- Efficacy of treatment
  - Difficult to assess because of the waxing and waning nature of alopecia areata.
  - Pediatricians should remind patients and families that this process is non-scarring and there is always the potential for full regrowth.
  - It is hoped that further elucidation of the genetics of alopecia areata will lead to more targeted therapies in the future.

Androgenetic Alopecia

- No therapy is reliably effective.
- Some patients may be helped by
  - Topical minoxidil twice daily
  - Hair transplant micrografts
- Finasteride
  - Can be given after 18 years of age in male patients
  - Contraindicated in female patients because of the possibility of genital defects in exposed male fetuses if a pregnancy occurs

Trichotillomania

- Petroleum jelly
  - The primary care pediatrician can paint the attacked areas in an attempt to frustrate the habit.
- Imipramine
- Fluoxetine
- Psychiatric intervention
  - Without attention to the possibility of an underlying emotional issue, other treatments are temporary.
  - Family structure and interaction with siblings and parents and with friends at home and at school should be explored in an effort to find stressors.
  - Consulting a psychiatrist should also be considered.
- Surgery or endoscopy
  - Referral for removal of a trichobezoar

Traumatic Alopecia

- Generally, simply discontinuing the stress will help.
- Injured hair follicles will often require ≥3 months to return to an anagen phase.

Loose Anagen Hair Syndrome

- Management is limited to reassurance and the passage of time.
- The hair eventually grows thicker and longer, and its pigmentation increases.

Tinea Capitis

- Topical antifungal agents do not provide adequate treatment because the fungus is deep in the follicle.
- Oral griseofulvin has been the standard of care.
  - The usual course of 2–3 months may present difficulties with adherence in a young child.
- Several newer agents have the appeal of offering a shorter course, despite their expense.
  - Terbinafine
    - This fungicidal drug appears effective when given for 6 weeks.
    - Currently approved for this use in children ≥4 years by the US Food and Drug Administration (FDA).
  - Itraconazole and fluconazole
    - May be safe for short courses in children but are not FDA approved for this use.
    - Have not proved effective for *Microsporum* tinea capitis.
    - Liquid itraconazole has been associated with diarrhea in children and with pancreatic adenocarcinoma in laboratory animals and should be avoided.
- Prednisone
  - Oral, tapered over 10 days
  - Rapidly decreases tenderness and inflammation of a kerion
  - Prevents widespread id reaction
- Secondary infection
  - With *M canis* or after treatment with an irritant.
  - Inflammation may require treatment with an antibiotic.

Lupus Erythematosus

- Discoid variant
  - Early treatment with topical or intralesional steroids may prevent scarring.
- Systemic variant
  - Loss of hair is generally temporary.

Acrodermatitis Enteropathica

- Oral zinc sulfate is the treatment of choice.

WHEN TO REFER

- Rapid, diffuse hair loss
- Chronic, progressive, localized, or diffuse hair loss without regrowth
- Scarring alopecia
- Inability to grow hair as a result of breakage, loss, or abnormal texture of hair
- Appearance of scalp mass or plaque affecting localized hair loss
- Plastic surgery
  - Expertise should be sought for consideration of hair transplants and scalp reduction (for scarred areas) when possible.

FOLLOW-UP

- Liver function testing
  - If antifungal medications are used for >12 weeks
  - At the start of therapy if any suggestion of preexisting liver disease exists

PROGNOSIS

- The possibility that hair will not fully regrow must be considered when loss
  - Follows high fever (telogen effluvium) or chronic toxicity (anagen effluvium)
  - Is accompanied by scarring
  - Occurs in the areas of
    - Nevi
    - Aplasia cutis
    - Persistent hemangioma
- Prognosis for the return of hair depends on
  - Elimination of the toxic stimulus
  - Whether the loss is accompanied by scarring
    - Loss associated with non-scarring conditions is recoverable.
    - Loss with scarring (eg, from iatrogenic scalp injury during delivery, from a burn) is permanent.
- Alopecia areata
  - The more extensive the loss and the younger the child, the less likelihood there is of a full recovery.
  - The disease is non-scarring and there is always the potential for full regrowth.
  - Prognosis is best when
    - Loss is less widespread.
    - Only 1 or 2 patches are present.
  - When hair does regrow, it may initially be white.
    - Eventually, color returns, and casual observers cannot identify the formerly affected area.
- Telogen effluvium
  - Telogen effluvium is generally reversible.
- Traumatic alopecia
  - In childhood, the hair will usually return, although regrowth can be slow.
- Loose anagen hair syndrome
  - After recovery and even into adulthood, the hair may still pull out easily and painlessly.
- Lupus erythematosus
  - Discoid variant
    - Hair loss can be permanent.
  - Systemic variant
    - Loss of hair is generally temporary.
    - There is no scarring, unlike in discoid disease.

PREVENTION

- Hair is fragile.
  - It should be handled gently and without physical or chemical assault.
  - In children, hair is probably best left alone, except for
    - Simple washing
    - Simple cutting

Amenorrhea

DEFINITION

- Amenorrhea is the absence of menses.
  - Primary amenorrhea: failure to start menstruation.
  - Secondary amenorrhea: cessation of menses in an adolescent who has previously menstruated.
  - Many diseases and clinical states may cause primary or secondary amenorrhea.

WHEN TO EVALUATE

- Abrupt cessation of menstruation in a teenager who has established regular cycles is of greater concern than the absence of menses for 3–4 months in a teenager who has a gynecologic age of 6 months–1 year.
- The point at which the clinician elects to pursue an evaluation depends on
  - Anxiety of the patient and her family
  - Possibility of pregnancy
  - Likelihood that a potentially serious disease is responsible for the amenorrhea
- Evaluation is warranted when
  - No signs of secondary sexual development are present by 14 years of age.
    - — Evaluation should include an assessment for delayed puberty.
  - Menarche has not occurred by 16 years of age, even if growth is normal and secondary sexual characteristics have developed.
  - Menarche has not occurred and the patient has been at Tanner stage 5 for at least 1 year or has had breast development for 4 years.
  - 3 consecutive menstrual cycles are absent in a patient with signs of an eating disorder.
  - A patient who has previously menstruated has had amenorrhea for >6 months.
  - The patient has not had menses and has symptoms or stigmata of another disease process, such as Turner syndrome.
  - The patient has had menstrual cycles, has missed one period, and has had unprotected sexual intercourse in the interim.
    - — In this instance, the patient should be evaluated for pregnancy.
  - Development has halted.

HISTORY

- Given the broad differential diagnosis for amenorrhea, many factors must be assessed.
- Menstrual history
  - Age at onset of menstruation
  - Bleeding frequency, duration, regularity, amount (number of pads/tampons and saturation)
  - Dates of previous menses
  - Concurrent symptoms (bloating, cramping, headaches)
- Menstrual history of mother and first-degree female relatives
- Pregnancy should be the primary consideration in patients with a history of sexual intercourse.
  - Denial of sexual activity by an adolescent does not exclude pregnancy.
- Medical and family history, including
  - Trauma
  - Endocrine disorders
  - History of meningitis or tumor
  - Irradiation
  - Surgery
  - Weight changes and growth patterns
- A history of uterine surgery or abortion raises the possibility of uterine synechiae.
- Detailed discussions of personal lifestyle factors are ideally conducted without others present.
  - HEADSSS assessment
    - — **H**ome
    - — **E**ducation
    - — **A**ctivities
    - — **D**rugs
    - — **S**exuality
    - — **S**uicide/Depression
    - — **S**afety
  - Exercise patterns
  - Body image; subtle development of physical features, such as weight gain, acne, or hirsutism

PHYSICAL EXAMINATION

- Vital signs
  - Evaluate blood pressure.
    - — High blood pressure may indicate renal disease or Cushing syndrome.
    - — Low blood pressure may indicate Addison disease.
  - Plot previous growth data (especially height, weight, and body mass index).
    - — Leveling of linear growth may be consistent with hypothyroidism.
    - — Growth failure may be consistent with inflammatory bowel disease.

  - Short stature may be consistent with Turner syndrome.
  - Extremes of body mass index may suggest the diagnosis (eg, anorexia, female athlete triad, Cushing syndrome, Prader-Willi syndrome).
- Physical examination
  - A complete examination is indicated.
  - Examine sexual development.
    - Assess the sexual maturity of breast and genitalia.
    - Atrophied breast tissue may suggest weight loss.
    - Pelvic examination is essential to evaluate female genitalia.
      - An imperforate hymen or a transverse vaginal septum may prevent menstrual blood from escaping.
      - If the hymenal opening is patent, the examination should proceed to determine the presence of a normal vagina, cervix, and uterus.
      - If the hymenal opening is very small, the cervix and uterus can be palpated by means of a bimanual rectoabdominal examination.
      - The size of the clitoris should be noted.
        - Clitoromegaly indicates the presence of excess androgens.
      - Lack of or scant pubic hair in a girl with Tanner stages 3–4 breast development suggests androgen insensitivity syndrome.
  - Examine for features of genetic conditions.
    - A webbed neck, short stature, and widely spaced nipples suggest Turner syndrome.
  - Examine for features of endocrine disorders.
    - Hirsutism, receding hairline, excessive acne, moon facies, striae, thyroid abnormalities, buffalo hump.
    - Acanthosis nigricans suggests insulin resistance.
    - Nipple discharge may indicate elevated prolactin levels.
  - Examine for neurologic abnormalities indicative of potential central nervous system (CNS) malformation or tumor.
    - Pupils, extraocular muscles, visual fields, smell, and cranial nerve functions
    - Funduscopy to look for papilledema
    - Reflexes
  - Examine for evidence of self-inflicted injury.
    - Cuts, burns, scars

DIFFERENTIAL DIAGNOSIS

- The differential diagnosis for amenorrhea is broad and includes
  - Pregnancy
  - Immature hypothalamic-pituitary-ovarian axis
    - Familial-physiologic delay
  - Suppressed hypothalamic-pituitary-ovarian axis
    - Eating disorders (including anorexia nervosa)
    - Drugs (eg, hormonal contraception, cocaine, phenothiazines)
    - Systemic factors
      - Acute illness (includes viral illness)
      - Chronic illness (includes inflammatory bowel disease, renal failure)
      - Depression
      - Psychosocial stress
      - Environmental change (eg, transitioning to college)
      - High-level athletic training (eg, female athlete triad)
    - Endocrine-related cause
      - Thyroid
        - Hyperthyroidism
        - Hypothyroidism
      - Adrenal
        - Addison disease
        - Cushing syndrome
        - Late-onset congenital adrenal hyperplasia (21-hydroxylase deficiency)
        - Tumor
  - CNS-related (hypothalamic, pituitary) issues
    - Developmental defects (eg, Kallmann syndrome)
    - Infiltrative disease
    - Head trauma
    - Sheehan syndrome (postpartum hypopituitarism)
    - Primary empty sella syndrome
    - Changes from prior meningitis
    - Irradiation
    - Surgery
    - Tumor (eg, prolactinoma)
  - Ovarian malfunction
    - Gonadal dysgenesis
    - Ovarian failure
    - Radiation or chemotherapy
    - Ovarian removal or destruction
    - Polycystic ovary syndrome (PCOS)
    - Tumor

A

- Genetic conditions
  - Laurence-Moon or Bardet-Biedl syndrome
  - Prader-Willi syndrome
  - Turner syndrome
- Outlet obstruction (primary amenorrhea)
  - Uterus
    - Uterine synechiae
    - Congenital abnormalities (müllerian agenesis, androgen insensitivity)
  - Vagina, cervix, hymen
    - Agenesis
    - Imperforate hymen
    - Transverse septum

LABORATORY EVALUATION

- For primary amenorrhea
  - Consider imaging as indicated before laboratory workup.
  - Consider karyotyping and serum testosterone measurement in a patient without a uterus to screen for müllerian agenesis or androgen insensitivity syndrome.
- If a uterus is present, or when considering secondary amenorrhea
  - Obtain urine pregnancy test and consider toxicology studies.
  - If negative result, obtain follicle-stimulating hormone (FSH), prolactin, and thyroid studies.
- If the FSH level is elevated, consider ovarian failure and consider karyotyping and screening for endocrinopathies.
- If the FSH level is low or normal, consider a physiologic, hypothalamic, or pituitary cause and chronic illness.
- If amenorrhea is in context of androgen excess, consider PCOS and late-onset congenital adrenal hyperplasia.
  - Serum testosterone (total and free)
  - Dehydroepiandrosterone (DHEA) and its sulfate (DHEA-S)
    - If the DHEA-S level is elevated, obtain a first morning 17-hydroxyprogesterone level.
  - Isolated elevated testosterone suggests an ovarian origin, whereas elevated DHEA-S suggests an adrenal origin.
- Assess the patient's estrogen status.
  - Measure serum estradiol levels, *or*
  - Assess by progesterone challenge or by vaginal maturation index (see Diagnostic Procedures section).
- In the case of eating disorders, consider a more thorough metabolic and functional evaluation.

IMAGING

- Imaging studies may be considered as clinically indicated.
  - Consider adrenal/ovarian imaging when the patient has
    - Evidence of virilization (eg, clitoromegaly)
    - Serum androgen levels elevated in the tumor range
  - Consider pelvic ultrasonography if
    - Pelvic or rectoabdominal examination cannot confirm the presence or absence of a uterus.
    - Bimanual examination is abnormal.
  - Consider magnetic resonance imaging if
    - Congenital abnormalities are suspected.
  - Consider dual-energy x-ray absorptiometry to evaluate bone density if
    - Estrogen levels are low.

DIAGNOSTIC PROCEDURES

- Assess the patient's estrogen status.
  - By progesterone challenge
    - A positive result indicates an estrogen-primed uterus.
    - Administer 10 mg of medroxyprogesterone acetate for 5–10 days.
    - Any spotting or bleeding in the week afterward is considered a positive result.
    - Some experts recommend measuring FSH level before performing a progesterone challenge.
      - Women with hypergonadotropic amenorrhea will have withdrawal bleeding.
  - By vaginal maturation index
    - A vaginal maturation index is performed by collecting cells from the upper lateral sidewall of the vaginal wall using a moistened cotton-tipped applicator.
      - Rolled on a glass slide.
      - Fixed by using the same technique as for Papanicolaou test preparation.
      - Samples can be interpreted on the basis of estrogen and pubertal status.

TREATMENT APPROACH

- Treatment of amenorrhea depends on the underlying cause.
- Adolescent girls can be reassured that they should anticipate menarche 2–3 years after the initiation of puberty when
  - Puberty starts late, but progression through puberty appears normal.
  - Physical examination is also normal.
  - This is especially likely with a family history of late menarche in first-degree female relatives.

SPECIFIC TREATMENT

Pharmacologic Treatments

- Secondary amenorrhea and normal estrogen levels
  - Medroxyprogesterone, 5–10 mg for 12–14 days
  - Can be used every 1–3 months to stimulate withdrawal bleeding
- Sexually active patients with PCOS
  - Treat with combined contraceptives.
- Patients with PCOS may benefit from additional medications for
  - Underlying metabolic abnormalities
  - Hirsutism, acne, or other findings associated with androgen excess

Other

- In some patients with low estrogen levels (restrictive eating disorders, female athlete triad)
  - Normalizing weight for height is important.
  - Address disordered eating and intensity of athletic training.

WHEN TO REFER

- If the amenorrhea seems to be secondary to a chronic illness that the pediatrician cannot manage
- If the pediatrician cannot offer or feels uncomfortable performing a thorough gynecologic assessment
- If long-term hormonal therapy is required
- If the patient has an eating disorder
- If evidence exists of anatomic or chromosomal abnormality
- If evidence exists of a complicated endocrine or developmental disorder
- If evidence exists of a CNS, adrenal, or ovarian tumor
- If the patient is pregnant and the pediatrician is unwilling or unable to offer counseling or referral for all options

WHEN TO ADMIT

- If the patient has metabolic derangements requiring close monitoring

FOLLOW-UP

- Regularly scheduled follow-up visits are warranted until menarche occurs.

Anemia and Pallor

DEFINITION

- Anemia is a laboratory finding reflecting a decrease in red blood cell (RBC) mass below an age-appropriate reference value; this can be any of the following conditions:
  - Reduction in RBC number
  - Reduction in RBC mass (hematocrit)
  - Reduced hemoglobin concentration
- Anemia may be associated with pallor but is more likely to be a silent symptom.
- Pallor and anemia are clinical manifestations of an underlying disease process requiring a thorough evaluation.
- Types of anemia
  - Microcytic anemias: mean corpuscular volume (MCV) less than appropriate for age
  - Normocytic anemias: MCV within reference range for age
  - Macrocytic anemias: MCV greater than appropriate for age
- MCV changes with age; see Laboratory Evaluation section for reference values.

HISTORY

- Thorough history may help identify risk as well as cause.
- Diet can identify children most likely to develop iron deficiency anemia.
- Signs of systemic illness (fever, weight loss) with anemia may indicate underlying systemic disease, such as an autoimmune disorder.
- Historical factors important for diagnosis of anemia include
  - Age
    - Nutritional anemias are rare in term infants but more common in infants born preterm, toddlers, school-aged children, and adolescents.
    - Significant anemia diagnosed in the first 6 months of life in a term infant is most likely due to a congenital anemia.
  - Sex
    - Glucose-6-phosphate dehydrogenase (G6PD) deficiency and pyruvate kinase deficiency are X-linked disorders.
  - Race/ethnicity
    - Thalassemias are more common in patients of African or Asian descent, whereas thalassemia syndromes are more common in patients of Mediterranean descent. Sickle cell anemia is most common in patients from Africa, South or Central America, Caribbean islands, Mediterranean countries, India, and Saudi Arabia.
  - Nutrition
    - Sources of iron, folate, vitamin B_{12}, and vitamin E should be documented.
    - A history of pica suggests iron deficiency.
  - Medications
    - Phenytoin and methotrexate can induce a megaloblastic anemia.
    - Oxidants can induce hemolytic anemias.
    - Sulfa drugs can produce a hemolytic anemia in patients with G6PD deficiency.
  - Family history
    - Anemia, jaundice, gallstones, cholecystitis, splenomegaly, splenectomy, or hemolytic crisis may suggest an inherited hemolytic anemia.
  - Infections
    - Infections may induce hemolysis or RBC hypoplasia or aplasia (parvovirus B19).
    - Hepatitis may induce aplastic anemia.
    - Common acute bacterial and viral infections may result in mild anemia from decreased RBC production or increased RBC destruction, or both.
      - These anemias are typically short lived but commonly identified on routine screening.
  - Gastrointestinal
    - The gastrointestinal tract is a common source of blood loss.
    - Nutritional deficiencies may result from malabsorption syndromes.

PHYSICAL EXAMINATION

- Most mild/moderate anemias are asymptomatic.
- Possible symptoms of anemia include
  - Infants and toddlers
    - Fatigue
    - Irritability
    - Pallor
    - Increased sleep
    - Poor feeding
    - Failure to thrive
  - Older children and adolescents
    - Fatigue
    - Pallor
    - Exercise intolerance
    - Dizziness
    - Headaches
    - Shortness of breath
    - Palpitations

- Pallor
  - Rare in mild anemias but common in children with moderate to severe anemia
  - Does not necessarily indicate a low hemoglobin level
  - Seen predictably only with hemoglobin concentrations <8 g/dL
  - May be more easily identified in nail beds, mucosa, conjunctiva, and palmar creases
- Signs of hemolytic anemia
  - Splenomegaly
  - Icterus
- Signs of chronic hemolytic anemia (eg, thalassemia)
  - Frontal bossing
  - Maxillary prominence
- Leukemia or lymphoma may present with anemia with focal lymphadenopathy and hepatosplenomegaly.
- Cardiovascular signs include
  - Mild to moderate decrease in RBC mass may result in pulmonary flow murmur.
  - More severe anemias may be associated with signs of congestive heart failure.

DIFFERENTIAL DIAGNOSIS

Utility of Subclassification

- Subclassification of anemias as microcytic, normocytic, and macrocytic greatly reduces the differential diagnosis and limits the number of laboratory tests needed for diagnosis.

Anemia in Newborns

- Classifying the cause into 1 of 3 broad classifications is helpful.
  - Blood loss
    - Twin-to-twin transfusions
    - Chronic blood loss throughout pregnancy
      - Newborn may have pallor and microcytic, hypochromic anemia but appear otherwise well and hemodynamically stable.
    - Newborns with acute blood loss
      - May have pallor, tachypnea, tachycardia, hypotension, and decreased tone.
      - Normocytic, normochromic anemia with a reticulocytosis will be detectable soon after birth.
  - Hemolysis
    - Different maternal blood types or antigens, maternal drug use, or neonatal infections.
      - Microangiopathic hemolysis may occur in newborns with thrombi, disseminated intravascular coagulation, and Kasabach-Merritt syndrome (multiple cavernous hemangiomas).
  - Decreased production in conditions such as Diamond-Blackfan or bone marrow suppression due to infection with parvovirus B19

Differential Diagnosis of Specific Pathologic Red Blood Cell Features[1]

- Frequently, normal blood smears will contain abnormal-appearing RBCs that are simply an artifact of trauma during the blood draw or ex vivo processing of the blood.
- Target cells: Surface to volume ratio is increased.
  - Thalassemia
  - Hemoglobinopathies
  - Hemoglobin C disease
  - Hemoglobin E disease
  - Hyposplenism or postsplenectomy
  - Hepatic disease
  - Severe iron deficiency anemia
  - Abetalipoproteinemia
  - Lecithin or cholesterol acyltransferase deficiency
- Spherocytes: hyperdense cells with a decreased surface to volume ratio and an increased mean corpuscular hemoglobin concentration.
  - Hereditary spherocytosis
  - Hemolytic anemia (autoimmune, ABO incompatibility, water dilution)
  - Microangiopathic hemolytic anemia
  - Hemoglobin SS disease
  - Hypersplenism
  - Burns
  - After RBC transfusions
  - Pyruvate kinase deficiency
- Acanthocytes (spur cells): cells with 10–15 spicules that are typically irregular in length, spacing, and width; cells usually smaller than normal RBCs.
  - Disseminated intravascular coagulation
  - Microangiopathic hemolytic anemia
  - Hyposplenism or postsplenectomy
  - Hepatic disease
  - Hypothyroidism
  - Vitamin E deficiency
  - Abetalipoproteinemia
  - Malabsorption

- Echinocytes (burr cells): cells with 10–30 spicules that are typically of similar size and distributed evenly.
  - Dehydration
  - Renal disease
  - Hepatic disease
  - Pyruvate kinase deficiency
  - Peptic ulcer disease
  - After RBC transfusion
- Pyknocytes: hyperchromic RBCs with decreased volume and distorted shape.
  - Similar to acanthocytes and echinocytes
- Blister cells: contain a clear area in RBCs that contains no hemoglobin.
  - Hemoglobin SS disease
  - G6PD deficiency
  - Pulmonary emboli
- Basophilic stippling: retention of RNA, resulting in fine blue inclusions in the cytoplasm.
  - Iron deficiency anemia
  - Lead poisoning
  - Hemolytic anemias
  - Pyrimidine 5'-nucleotidase deficiency
- Elliptocytes: elliptical-shaped cells.
  - Hereditary elliptocytosis
  - Iron deficiency anemia
  - Thalassemia
  - Hemoglobin SS disease
  - Sepsis
  - Megaloblastic anemia
  - Malaria
  - Leukoerythroblastic reaction
- Teardrop cells (dacryocytes): microcytic and hypochromic cells that are teardrop shaped.
  - Normal finding in newborns
  - Thalassemia
  - Myeloproliferative diseases
  - Leukoerythroblastic reaction
- Schistocytes: RBC fragments that result from trauma.
  - Disseminated intravascular coagulation
  - Hemolytic anemia and microangiopathic hemolytic anemia
  - Kasabach-Merritt syndrome
  - Purpura fulminans
  - Hemolytic uremic syndrome
  - Uremia, glomerulonephritis, acute tubular necrosis
  - Cirrhosis
  - Malignant hypertension
  - Thrombosis
  - Thrombotic thrombocytopenic purpura
  - Amyloidosis
  - Chronic relapsing schistocytic hemolytic anemia
  - Burns
  - Connective tissue disorders
- Stomatocyte: area of central pallor is more slit-like than round.
  - Stomatocytosis (hereditary)
  - Thalassemia
- Nucleated RBCs: normal on peripheral blood smear in the first week of life only.
  - Significant bone marrow stimulation
  - Congenital infections
  - Hyposplenism or postsplenectomy
  - Leukoerythroblastic reaction, particularly with severe infections and leukemias or metastatic tumors in the bone marrow
  - Megaloblastic anemia
  - Dyserythropoietic anemia

LABORATORY EVALUATION

- Tests to perform
  - Hemoglobin level and hematocrit.
  - RBC morphology (see Differential Diagnosis section).
  - MCV.
  - Reticulocyte count.
    - Elevated count implies bone marrow compensation for chronic blood loss or hemolysis.
    - Low count (<1%) may suggest impaired RBC production or acute blood loss.
  - Stool guaiac tests for occult blood should be performed at several different times to capture intermittent bleeding.
  - The following tests are not necessary in initial diagnosis but help identify cause:
    - Iron studies
    - Erythrocyte sedimentation rate
    - Serum bilirubin
    - Serum lactate dehydrogenase
- Mean reference values for hemoglobin (g/dL)/hematocrit (%)/MCV (mcm^3), by age.
  - Cord blood: 15.3/49/112
  - 1 day: 19.0/61/119
  - 1 week: 17.9/56/119
  - 1 month: 17.3/54/112
  - 2 months: 10.7/33/100
  - 3 months: 11.3/33/88
  - 6 months–2 years: 12.5/37/77
  - 2–4 years: 12.5/38/79
  - 5–7 years: 13/39/81
  - 8–11 years: 13.5/40/83
  - 12–14 years
    - Girls: 13.5/41/85
    - Boys: 14/43/84

- 15–17 years
  - Girls: 14/41/87
  - Boys: 15/46/86

- Black children, on average, have reference hemoglobin values that are ~0.5 g/dL lower than those in white and Asian children.
- α-Thalassemia trait is the result of mutation in 2 genes.
  - Molecular genetic testing of *HBA1* and *HBA2* detects deletions in about 90% and point mutations in about 10% of affected individuals.
  - For genetic counseling the typical Asian genotype with both abnormal genes on the same chromosome is of greater concern than the usual genotype in black patients with one abnormal gene on each chromosome.

IMAGING

- Chest radiograph may be required if pulmonary hemosiderosis needs to be ruled out.

DIAGNOSTIC PROCEDURES

- Bone marrow aspiration and biopsy may be required in patients with anemia suspected of having bone marrow involvement or abnormalities.

TREATMENT APPROACH

- Treatment of compensated anemia is dictated by the cause of the anemia.
- Patients with uncompensated anemia should be admitted to the hospital for observation and possible transfusion.
- Many patients with microcytic anemia or normocytic anemia have early iron deficiency anemia, and a course of supplemental iron is appropriate.

SPECIFIC TREATMENT

- Specific treatment depends on the underlying hematologic disorder.
- For a child with hypochromic, microcytic anemia found on routine blood cell count with history of poor iron intake or excessive milk intake
  - Give a trial of supplemental iron (3–6 mg/kg of elemental iron per day, divided into ≥2 doses) rather than drawing additional blood for analysis.
    - Reticulocyte count should increase within 5–7 days.
    - Assuming that the dietary deficiency is corrected, supplemental iron should continue for 2–3 months after the hemoglobin concentration has normalized to fully replenish iron stores.
- Thalassemia major requires long-term transfusion therapy.

WHEN TO REFER

- Referral to hematologist.
  - Hemoglobin level <8 g/dL or hematocrit <25%
  - Anemia of unknown origin
  - When anemia is associated with disorder in leukocytes or platelets
  - If hemoglobinopathy or RBC membrane defect is suspected or confirmed
  - If no clear vitamin B_{12} or folate deficiency, for assessment of macrocytosis to rule out myelodysplasia or cancer
- Referral to a pediatric oncologist is warranted for management of most macrocytic anemias that are not related to nutritional deficiencies.

WHEN TO ADMIT

- Profound anemia (hemoglobin level <5)
- Uncompensated anemia or anemia associated with a rapidly decreasing hemoglobin level
- Anemia in an ill child

FOLLOW-UP

- Patients receiving a therapeutic trial of iron for suspected iron deficiency anemia should be followed up at 1 week for repeated measurement of the reticulocyte count or at 1 month for hemoglobin measurement.
  - If there is no change in reticulocyte count or hemoglobin level, consider noncompliance with therapy, a problem with iron assimilation, or another diagnosis for microcytic anemia.

COMPLICATIONS

- If iron deficiency is not diagnosed and treated early, it may adversely affect the cognitive function of the brain.

PREVENTION

- All infants are provided with iron-fortified food after 6 months of age.
- All infants are checked for hemoglobin and lead levels between 9 and 12 months of age.
- All children and adolescents, especially menstruating girls, need to be checked for hemoglobin and hematocrit yearly.

REFERENCE

1. Modified from Nathan DG, Orkin SH. A diagnostic approach to the anemic patient. In: *Nathan and Oski's Hematology of Infancy and Childhood*. 5th ed. Philadelphia, PA: WB Saunders; 1998

Animal Bites

DEFINITION

- Bites occur from dogs (most common), cats (second most common), humans, and wild animals.

SIGNS AND SYMPTOMS

- Important points to elicit while taking history include
  - Length of time since injury
  - Type of animal (including domestic or wild)
  - Whether the attack was provoked or unprovoked
  - Animal's present location
  - Immunization status and health
  - Prior wound management
- Animal bites from nondomestic animals require special attention.
  - Evaluate children who may have been exposed to rabies.
  - Know when to treat.
- Human bites can transmit HIV and hepatitis B virus.
  - Test for these in situations of high risk.
- Physical examination entails a thorough musculoskeletal and neurologic examination.
  - Determine whether underlying structures were damaged.
  - Inspect wound for signs of infection.
    - Pay special attention to the hand because superficial signs of infection (eg, redness, swelling, purulent drainage) may be absent.
  - Cellulitis
    - Due to *Pasteurella multocida*.
    - Generally develops rapidly, within hours of the animal bite.
    - Systemic signs (eg, fever, lymphangiitis) are usually absent.
    - Gradual development over days is more likely the result of gram-positive cocci or other pathogenic bacteria.
  - Cat-scratch disease is a common complication of cat bites and (less common) bites by other animals.
    - Begins with a red, painless papule at the site of the recent scratch or bite
    - Within weeks: tender, enlarged, regional lymph node, usually associated with fever, malaise, and other systemic symptoms

LABORATORY FINDINGS

- Gram stain of a wound specimen is not useful.
- Cultures of infected wounds
  - Have no growth in one-third of cases.
  - Do not predict the likelihood of subsequent infection.
  - May help ensure that the causative bacteria are sensitive to the antibiotic used.
- Cat-scratch disease
  - Caused by *Bartonella henselae*
  - Can be diagnosed clinically or confirmed by serologic testing

IMAGING

- Radiologic studies
  - May be necessary for deep puncture wounds to determine whether the periosteum has been penetrated.
  - Include the calvaria of small children who experience bites to the head.

TREATMENT APPROACH

- The initial step is meticulous wound care.
  - Gently clean the wound with soap and water.
  - Saline irrigation with a syringe and 19-gauge needle generates pressure on the tissues that facilitates cleansing and reduces risk of infection.
  - Devitalized tissue should be debrided.
  - Puncture wounds should be cleaned, but irrigation is ineffective and may result in further damage.
  - Elevation and immobilization are important for significant extremity injuries.
- The child's immunization status should be assessed and tetanus prophylaxis provided if indicated.
- Primary laceration closure is controversial.
  - Wounds that are clearly infected should not be closed.
  - Most noninfected lacerations can be sutured for cosmetic purposes or for hemostasis.
    - After meticulous cleansing and irrigation.
    - Hand wounds are the exception, owing to great likelihood of infection and risk of serious complications from deep, closed-space infections.
    - Suturing of the hand is suggested only for large wounds.

- Use of prophylactic antibiotics in noninfected bite wounds is controversial.
  - They are indicated after a human or animal bite to the hand.
  - No evidence indicates effectiveness for other types of cat and dog bites.
- Infected bite wounds brought to medical attention after 24 hours should be treated with antibiotics.
- For wild animal bites, consult with the local health department to determine the risk of rabies for particular geographic region.
  - Bats, skunks, foxes, raccoons, and other carnivores are considered rabid until proved otherwise by laboratory tests.
  - In the interim, or if the animal cannot be found, treatment with human rabies immunoglobulin G (HRIG/RIG) and human diploid cell vaccine is suggested.
  - Rabies prophylaxis is now suggested after exposure to bats in a confined setting, even when no bites are visible.
    - Because the location of a bat bite is rarely known, HRIG/RIG dose may be given in the thigh.
    - If the bat can be captured and submitted for testing, rabies prophylaxis can be avoided in 60% of the cases.
- Approach for rabies is shown in **Table 1**.

SPECIFIC TREATMENTS

- Choice of antibiotics depends on culture results or, if cultures are not available, on the likely pathogens.
- Amoxicillin/clavulanic acid is an excellent choice for empirical treatment of bites from all animals.
- Penicillin is active against *P multocida* and many oral flora.
  - A penicillinase-resistant antibiotic provides more effective coverage.
- Penicillin-allergic children may be treated with extended-spectrum cephalosporin or trimethoprim-sulfamethoxazole plus clindamycin.
  - Doxycycline with activity against *P multocida* and methicillin-resistant *Staphylococcus aureus* provides another alternative in patients ≥8 years.
- Intravenous (IV) antibiotics
  - Indicated in patients with
    - Infected hand bites
    - Moderate to severe infections at other bite sites
    - Those who present with systemic symptoms, such as high fever
- Cat-scratch disease
  - Generally self-limited and does not benefit from antibiotics.
  - Large, tender, fluctuant lymph nodes may require aspiration or incision and drainage.

WHEN TO ADMIT

- Infected wounds requiring IV antibiotics
- Extensive facial wounds requiring skilled nursing care

WHEN TO REFER

- Complex wounds that require surgical repair
- Bites to the face or hand that require plastic surgery
- Infected wounds that do not respond to initial treatment
- Children with human bites from an adult

Table 1. Rabies Vaccination Guidelines

Animal	Management
Wild carnivores	Begin HRIG/RIG and HDCV. Submit animal's head for testing.
Healthy domestic dogs and cats	Quarantine animal; treat only if animal develops symptoms.
Stray or sick dogs and cats	Submit animal's head for testing. Delay treatment until test results are known unless clinical likelihood of rabies is high. If animal is unavailable, complete full series of HRIG/RIG and HDCV.
Rodents, rabbits	Unlikely to be rabid (except woodchucks). Treat only if animal acted strangely and cannot be tested.

Abbreviations: HDCV, human diploid cell vaccine; HRIG/RIG, human rabies immunoglobulin.

From Centers for Disease Control and Prevention. Human rabies prevention—United States, 1999. Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep.* 1999;48(RR-1):1–21.

FOLLOW-UP

- If the animal that caused the bite is quarantined because its rabies status is unknown, the animal and the bitten individual need close follow-up.

COMPLICATIONS

- Deep infections of tendons or bones and systemic infections can occur if animal bites go untreated.
- Major morbidity from animal bites results from direct trauma and infection.
- Dog bites can cause lacerations or avulsions if infected.
- Puncture wounds can result in deep-tissue infections.

PREVENTION

- Education about responsible pet care is important.
- Preschool-aged children
  - Should not be left alone with a pet
  - Should be advised never to tease animals, approach strange animals, or play with pets that are eating
- Families who have children should be advised not to buy wild animals or dogs bred for aggressiveness.
- Vaccinations for pets and routine visits to the veterinarian should be encouraged.
- Families traveling with children should be on the alert for stray animals in foreign countries.
  - If the family is planning to spend an extended period in a country with endemic rabies, prophylactic rabies vaccination should be strongly considered.

Anorexia Nervosa

DEFINITION

- Purposeful loss of weight beyond a healthy state.
- Intense fear of gaining weight or becoming fat, or persistent behavior that interferes with weight gain, even though underweight.
- Disturbance in perception of body weight or shape, undue influence of body weight or shape on self-evaluation, or persistent lack of recognition of the seriousness of current low body weight.
- Change to definition per *Diagnostic and Statistical Manual of Mental Disorders*, 5th Edition (*DSM-5*): Requirements that weight be ≥15% below "ideal body weight" (IBW) and have amenorrhea ≥3 months have been eliminated from diagnostic criteria.
- Restricting type
  - Weight loss accomplished primarily through dieting, fasting, and/or excessive exercise.
  - During the past 3 months, the individual has not regularly engaged in recurrent episodes of binge-eating or purging behavior (ie, self-induced vomiting or the misuse of laxatives, diuretics, or enemas).
- Binge-eating or purging type
  - During the past 3 months, the individual has engaged in recurrent episodes of binge-eating or purging behavior.
- Atypical type
  - All criteria for anorexia nervosa are met, except that despite significant weight loss, weight is within or above reference range.

SIGNS AND SYMPTOMS

- Concern about weight loss, vomiting, or abnormal eating attitudes noticed by family, friends, or school authorities
- Common for patients to be brought in against their will, although some seek help willingly
- Distorted body image
- History of bingeing or purging
- Overexercising
- Psychosocial changes
  - Fighting with family
  - Withdrawing from friends
  - Performing less optimally in school
  - Improved school performance due to withdrawal from friends and family
- Symptoms of malnutrition
  - Alopecia
  - Cold hands and feet
  - Dry skin
  - Constipation
  - Fatigue
  - Absence of ≥3 consecutive menstrual cycles
  - Scaphoid abdomen
  - Muscle wasting
  - Acrocyanosis
  - Decreased subcutaneous fat
  - Lanugo hair similar to that seen in newborns
  - Ecchymoses
  - Diminished reflexes
- Weight percentage below IBW
  - Calculated by comparing current weight with average weight expected for height, age, and sex (on standard pediatric growth charts)
  - Serves as diagnostic criterion and as gross estimate of the degree of malnutrition
    - Weight <25% below IBW: severe malnutrition
    - Weight 20% below IBW: moderate malnutrition
    - Weight not yet 20% below IBW: mild malnutrition
- Vital signs that show malnutrition
  - Decline in blood pressure
  - Decreased pulse
  - Cardiovascular changes
    - Decline in electrocardiogram (ECG) voltage
    - Sinus bradycardia
    - Prolonged QTc
    - Orthostatic hypotension
    - Increased vagal tone
    - Poor myocardial contractility
    - Mitral valve prolapse
    - Pericardial effusion
    - Decreased left ventricular mass

DIFFERENTIAL DIAGNOSIS

- Differential diagnosis of eating disorders includes possible causes of weight loss or vomiting and other psychiatric causes of poor appetite.
- Medical causes
  - Cancer
  - Central nervous system tumors
  - Gastrointestinal problems
    - Malabsorption
    - Celiac disease
    - Inflammatory bowel disease
  - Endocrinologic problems
    - Diabetes mellitus
    - Hyperthyroidism
    - Hypopituitarism
  - Chronic illnesses/infections
  - Superior mesenteric artery syndrome

- Psychiatric causes
  - Depression.
  - Obsessive-compulsive disorder.
  - Psychosis (especially schizophrenia).
  - Patients may have concomitant depression or psychosis; separate criteria must be used to establish each entity.
  - Sleep disorders.
  - Hallucinations, delusions, or obsessions.

DIAGNOSTIC APPROACH

- Physical examination
  - Measure height, weight, and vital signs.
  - Plot height, weight, and body mass index (BMI) on the patient's growth curve.
  - Calculate percentage below IBW.
- Distortion of body image is a hallmark of anorexia nervosa.
  - Evaluate by exploring the patient's views of initial, current, and desired weight.
- Establish patient's eating and exercise patterns.
- Obtain a full psychosocial history as part of initial evaluation.
- Assess use of vomiting or medications designed to promote weight loss.
  - Diet pills
  - Laxatives
  - Diuretics
  - Ipecac
- Avoid being misled by the patient who is not completely forthright; results of physical examination and laboratory tests often suggest the true extent of the disorder.
- For girls, a full menstrual history should be obtained.
  - Age at menarche
  - Last normal menstrual period
  - Usual length of menses
  - Heaviness of flow
  - Presence of dysmenorrhea
  - Regularity of menses
- Initial evaluation of weight loss includes
  - Determination of the diagnosis and its severity
  - Evaluation of other possible causes
  - Analysis of psychological context
  - Decision about treatment

LABORATORY FINDINGS

- Initially, laboratory results may be within reference ranges.
- Workup should include
  - Complete blood cell count
    - Leukopenia
    - Occasionally, thrombocytopenia
    - Rarely, severe anemia (Concomitant amenorrhea may protect from iron deficiency anemia.)
  - Serum electrolytes
    - Evidence of dehydration
      - Elevated sodium level
      - Elevated blood urea nitrogen level
    - Excessive drinking
      - Signs of hyponatremia
      - Dilute urine
    - Hypokalemia, often severe
    - Nutrient values that may be altered
      - Zinc
      - Calcium
      - Magnesium
      - Copper
      - Vitamin B_{12}
      - Folate
  - Hormone testing
    - Relative hypothyroidism caused by combination of euthyroid sick syndrome and decreased production on a hypothalamic basis
      - Low-normal levels of triiodothyronine, thyroxine, thyroid-stimulating hormone, or any combination
    - In patients with amenorrhea, low levels of
      - Luteinizing hormone
      - Follicle-stimulating hormone
      - Estradiol
      - Prolactin
    - Hypercortisolism with loss of diurnal variation
    - Low levels of insulin-like growth factor 1
    - Low levels of leptin
    - Increased ghrelin levels
    - Increased peptide YY levels
  - Liver and thyroid function tests
- Urinalysis for specific gravity and ketonuria is often helpful.

IMAGING

- Computed tomography and magnetic resonance imaging (MRI) of the brain
- Generally reserved for evaluating other possible causes when diagnosis is in question
- MRI changes including gray matter deficits and elevated cerebrospinal fluid volumes that may not be reversible
- Gastric emptying studies may show
  - Delayed gastric emptying
  - Decreased gastrointestinal motility
- Bone densitometry, using dual-energy x-ray absorptiometry
  - Bone density values are correlated with BMI, age at onset, and duration of illness.
  - Commonly used in evaluation of patients with eating disorders/amenorrhea of 6–12 months' duration

DIAGNOSTIC PROCEDURES

- ECG for persons with bradycardia
- To document orthostatic changes
  - Check blood pressure and pulse in the sitting position, followed by standing for 2 minutes.
  - Significant findings include
    - Increase of 20 beats/min in pulse
    - Decrease of 20 mm Hg in systolic blood pressure
    - Decrease of 10 mm Hg in diastolic blood pressure

TREATMENT APPROACH

- Medical and nutritional rehabilitation are crucial.
  - Restoration of body weight to within 10% of IBW, with restoration of menses, are primary goals.
  - If malnutrition is mild to moderate (15%–25% below IBW), restoration may be accomplished on an outpatient basis.
  - If malnutrition is moderate to severe (>25% below IBW), treatment usually requires hospitalization.
- Medical treatment includes management of
  - Electrolyte abnormalities
  - Cardiovascular issues
  - Endocrine disorders
  - Other organ system dysfunction
  - Managed simultaneously with or aided by nutritional rehabilitation
- Nutritional therapy
  - Daily intake of 3 substantial meals and 3–4 snacks is usually sufficient for required weight gain.
  - At inpatient units, meals are generally provided as part of a strict regimen, and snacks generally consist of high-calorie supplements.
  - Too-rapid weight gain is associated with severe metabolic abnormalities in some patients (refeeding syndrome).
  - Slow refeeding and phosphorus supplementation are required in severe malnutrition to prevent this syndrome (which can involve cardiac failure, hemolysis, coma, and death).
- A team approach is needed to treat disease; this may consist of
  - Primary care physician.
  - Psychiatrist.
  - Psychologist or social worker.
  - Nutritionist.
  - The exact combination is determined by local expertise, availability, and preference.
  - Team discussions are held frequently to prevent miscommunication.
- Treatment settings
  - Inpatient and residential
    - Patients are admitted for medically or psychiatrically emergent reasons.
    - Protocols are designed to ensure weight gain and to guard against refeeding syndrome.
    - Many begin with food, moving to oral supplements or nasogastric feeds if meals are not consistently consumed.
      - Some evidence suggests that using nasogastric tubes at the time of admission can increase the rate of weight gain.
    - After stabilization, patients are often transferred to residential programs with less medical monitoring and more psychological support.
    - Behavioral approaches include treatment phases based on achievement of progressively higher weight goals or improved behaviors or attitudes.
      - Each phase incorporates privileges into the patient's daily activities (eg, food choices, food preparation, passes for program outings, passes with family).

A

- Day programs and intensive outpatient programs
  - Day program
    - Patients ready to leave the residential setting are stepped down to a day program.
    - Generally 5 days per week, providing 2–3 meals and snacks daily.
  - Intensive outpatient program (IOP)
    - Step down again to IOP.
    - Generally 3 hours per day, 3 days per week, providing a meal and a group.
  - In both settings, patients live at home; patients in IOP can attend school.
  - Often, IOP and day programs are used as a step up from a general outpatient setting to avoid the next higher level of care.
- Outpatient, least intensive option, often includes
  - Medical monitoring
  - Nutritional support
  - Psychiatric support
  - Therapy (individual, family, and/or group therapy)

SPECIFIC TREATMENTS

Therapy Options

- Most common
  - Individual therapy
    - Varied
    - Difficult to study
  - Cognitive behavioral therapy
    - Decreasing nutritional restriction
    - Normalizing eating
    - Changing perceptions and overconcern with body weight and shape
  - Dialectical behavioral therapy
  - Family-based treatment (FBT)
    - Often called the "Maudsley approach."
    - No blame placed on parents or patient.
    - Parents need to manage the patient's eating because the patient has been unable to and the patient's health is in jeopardy.
    - Parents are empowered to refeed their child.
    - The entire family is involved in treatment.
    - Three phases
      - Refeeding by caregivers
      - Transferring eating responsibility back to the patient
      - Relapse prevention
    - Therapist needs to be trained in this method.
    - 50%–60% of patients are in remission by the end of the first year, 25%–35% practically recover, and 15% are resistant.
    - In comparison, <50% of patients who receive more traditional treatment recover within 2–5 years, one-third partially recover, and 20% are resistant.
    - FBT has become a first-line treatment when a trained therapist is available.

Psychopharmacologic Therapy

- Selective serotonin reuptake inhibitor (SSRI) antidepressant
  - Helps with concurrent psychiatric disorder.
  - Helps treat obsessive-compulsive symptoms.
  - Only physicians familiar with psychopharmacologic agents should prescribe these as part of treatment, given the potential for SSRIs to increase risk of suicide in a minority of children and adolescents.
  - Not effective in promoting weight gain or treating symptoms of depression or obsessive-compulsive disorder when body weight is low.
- Atypical antipsychotic agent at low doses can improve weight gain and treat symptoms of depression and obsessional thoughts.
- Menses restoration in those with amenorrhea
  - Generally requires estradiol level >30 mg/dL.
  - Estrogen replacement has not been shown to reverse or prevent bone loss.
  - Oral estrogen-progesterone combination pills are not effective in increasing bone density.
  - Physiologic estrogen replacement in the form of a transdermal patch along with cyclic progesterone increases rate of bone accrual in adolescents with anorexia nervosa to the level of age-matched controls.
  - Regaining weight is the only definitive treatment to bring about the return of menses.

Dietary Plan

- In outpatients
  - May be developed on the basis of patient's and family's prior eating habits or on a specific dietary plan offered by the physician, a nutritionist, or parents if they are in family-based treatments.
  - Should be specific to avoid ambiguities that can lead to family fighting.
  - Should provide 2,000–3,000 calories a day.
    - May include high-calorie supplements

- Should be balanced and include foods from each of the major food groups.
- Weight gain should be 1–2 lb per week (inpatient gains may be 2–4 lb per week).
- Compliance with dietary regimen may be evaluated by having the patient keep a diet diary; however, many patients do not keep accurate and honest records.

WHEN TO ADMIT

- <75% IBW or ongoing weight loss despite intensive management
- Refusal to eat
- Body fat <10%
- Heart rate <50 beats/min daytime; <45 beats/min nighttime
- Systolic pressure <90 mm Hg
- Orthostatic changes in pulse (>20 beats/min) or blood pressure (>10 mm Hg)
- Temperature <36°C (96°F)
- Arrhythmia

WHEN TO REFER

- A team approach is most often used.
- If patient is medically stable, refer to a therapist skilled in FBT, if available.
  - If not, refer to a dietitian to reinforce primary care physician's nutritional recommendations or to set a nutritional plan if he or she does not have the expertise or time to do so.
- Refer to a psychotherapist if
  - The patient is open to therapy.
  - The patient cannot attain goals set by the physician, even if the patient is resistant.
- Refer for psychopharmacologic evaluation if
  - The physician and therapist believe the patient might benefit from medication.
  - Patient is bingeing and open to medication.
  - Obsessive-compulsive symptoms are interfering with treatment.
- Refer to adolescent medicine specialist if
  - The primary care physician is not comfortable treating the patient.
  - The physician cannot provide sufficient time for patient needs.
  - The patient does not adhere to the treatment plan.

COMPLICATIONS

- Acrocyanosis
- Alopecia
- Dry skin
- Lanugo
- Ecchymosis
- Fatigue
- Hypothermia
- Muscle wasting
- Bloating
- Postprandial fullness
- Decreased subcutaneous fat
- Decreased deep-tendon reflexes
- Constipation
- Delayed gastric emptying
- Delayed gastric motility
- Orthostatic hypotension (change in heart rate >20 beats/min, change in blood pressure >10 mm Hg)
- Bradycardia
- Mitral valve prolapse
- Pericardial effusion
- Electrocardiographic abnormalities, including prolonged QT interval
- Decreased left ventricular mass and contractility
- Psychomotor retardation
- Growth delay
- Pubertal delay
- Amenorrhea or menstrual irregularity
- Osteopenia, osteoporosis
- Cortical atrophy on MRI
- Electrolyte abnormalities from water loading or purging
- Hypercholesterolemia without hyperlipidemia
- Euthyroid sick syndrome
- Low luteinizing hormone, follicle-stimulating hormone, prolactin
- Elevated cortisol level
- Low insulin-like growth factor 1
- Low leptin

PROGNOSIS

- Adolescents with severe anorexia nervosa have a protracted disease course; recovery estimates 10–15 years later vary from 76% to 24%.
- ~50% of patients do well in the long term.
- 30% show varying degrees of improvement.
- 20% do poorly despite adequate treatment.
- Patients who are younger or have milder disease fare better.
- Predictors of poorer outcome
  - Older age.
  - Vomiting.
  - Premorbid personality problems.
  - Any patient with these may do well with treatment.

- Mortality is higher than in any other psychiatric illness—≤5% per decade after the onset of the eating disorder.

PREVENTION

- Best preventive strategies are not clear.
- Increasing evidence that eating disorder and obesity may be related, with dieting, weight-related teasing, and body dissatisfaction as risk factors; therefore, an integrated approach to prevention is sensible.
- Early detection is most effective.
  - Earlier treatment is easier while the disease is less entrenched.
  - Families, friends, school personnel, and health professionals must be vigilant for signs and symptoms of an eating disorder.
- Programs are geared toward teenaged boys and girls, primarily in school settings.
  - Maintenance of healthy body image and healthy eating.
  - Promotion of self-esteem without relation to weight.
  - Programs seem to succeed in terms of increased awareness and knowledge about eating disorders.
    - Overall effectiveness is debatable.
- Classroom interventions
  - Staff training throughout the school
  - Informal discussions between staff and students
  - Integration of material about eating issues into the curriculum
  - More intensive work with persons at high risk
  - Changes within the school with respect to cafeteria food and physical education
  - Referrals and outreach (in school and community)

Anuria and Oliguria

DEFINITION

- Oliguria is decreased urine output.
  - Newborns and infants: <0.5 mL/kg/h for 24 hours
  - Older children: <500 mL/1.73 m^2 body surface area per day
- Anuria is absence of any urine output.
  - Normal, healthy newborns may have no urine output for 24 hours after birth.
- Oliguria is much more common than anuria but can lead to anuria, resulting in serious renal damage that requires specialized care.

SIGNS AND SYMPTOMS

- Clinicians need to search for specific signs of underlying renal disease.
  - Severe anemia due to hemolytic uremic syndrome
  - Butterfly rash on face/musculoskeletal involvement in systemic lupus erythematosus
  - Purpuric rash over buttocks and extensor surface of lower extremity in Henoch-Schönlein purpura
  - Palpable kidney may be due to
    - Renal vein thrombosis
    - Polycystic kidney disease
    - Multicystic dysplastic kidney
    - Hydronephrosis
- Palpable bladder with weak urine stream or dribbling suggests bladder neck or urethral obstruction.
- Sacral tuft of hair or myelomeningocele may be seen with neurogenic bladder (can cause obstructive uropathy/postrenal oliguria or anuria).
- Symptoms of prerenal cause
  - Vomiting
  - Diarrhea
  - Hemorrhage
  - Sepsis
  - Decreased oral intake
  - Increased thirst
  - Palpitations
  - Fatigue
  - Clinical signs of dehydration
  - Weight loss
- Symptoms of hypovolemia (ie, prerenal pathology)
  - Tachycardia
  - Dry mucous membranes
  - Sunken eyes
  - Orthostatic blood pressure changes
  - Decreased skin turgor
  - Hypotension
- Symptoms of intrinsic renal disease
  - Gross hematuria
    - Pharyngitis or impetigo a few weeks before the onset of gross hematuria
  - Hypertension
  - Edema
  - Bloody diarrhea
    - Often precedes hemolytic uremic syndrome
  - Younger children, particularly neonates and infants: signs of congestive heart failure
    - Hepatomegaly
    - Gallop rhythm
    - Pulmonary edema
- Symptoms of systemic vasculitis (eg, systemic lupus erythematosus)
  - May see history of fever, joint pains, and skin rash
- Recurrent sinusitis or lower respiratory tract infections may suggest Wegener granulomatosis.
- Hemoptysis may indicate pulmonary renal syndrome, due to either
  - Goodpasture syndrome
  - Microscopic polyangiitis

DIAGNOSTIC APPROACH

- Thorough history and physical examination are important in identifying the cause of oliguria or anuria.
  - Comprehensive physical examination is key to assessing severity of the disease process and possible cause.
  - In prerenal and postrenal acute kidney injury, early diagnosis and prompt treatment often result in quick recovery.
- Detailed history of recent or ongoing long-term medication use is important for excluding possible interstitial nephritis.
- In neonates, history of umbilical artery catheterization implies renal artery thrombosis.
- Family history is helpful in diagnosing such conditions as diabetes insipidus and polycystic kidney disease.

LABORATORY FINDINGS

- Risk factors, history, and results of physical examination will help in the selection of appropriate laboratory tests.
- Urinalysis is the most important noninvasive diagnostic test.
  - Thorough examination of a freshly voided or bladder-catheterized urine sample helps distinguish prerenal from renal causes.
    - Normal or near-normal urinalysis, with few cells, few or no casts, or little or no proteinuria, is seen in prerenal disease, obstruction, and some cases of acute tubular necrosis.
    - A sample showing muddy-brown granular casts and epithelial cell casts strongly suggests acute tubular necrosis.
    - Erythrocyte casts are diagnostic of glomerulonephritis.
    - Significant proteinuria indicates glomerular disease.
- Urinary indexes are important for diagnosis of oliguria.
  - Urinary sodium
    - <10 mEq/L in oliguria resulting from intravascular volume depletion.
    - Neonates: Prerenal disease is associated with urine sodium concentration <20–30 mEq/L.
  - Specific gravity
    - >1,020 *g* in prerenal oliguria
  - Creatinine
    - Urine/plasma creatinine ratio >40 in prerenal oliguria
    - Urine/plasma creatinine ratio <20 if renal cause
  - Osmolality
    - Urine/plasma osmolality >1.5 in prerenal oliguria
    - Urine/plasma osmolality <1.5 if renal cause
- Fractional excretion of sodium
  - <1% suggests reabsorption of almost all filtered sodium in response to decreased renal perfusion (prerenal).
  - In acute tubular necrosis: >2%.
  - Newborns and young infants cannot establish <2% even in prerenal acute kidney injury.
- Blood urea nitrogen (BUN) and serum creatinine
  - In prerenal oliguria, increased BUN level is marked and the BUN/serum creatinine ratio is >20.
  - BUN/creatinine ratio of 10–15 suggests intrinsic renal damage.

IMAGING

- Renal ultrasonography
  - Generally not indicated in children with prerenal failure from dehydration who respond promptly to fluid resuscitation.
  - Provides important information about
    - Kidney size and echogenicity
    - Renal blood flow
    - Collecting system
    - Urinary bladder
  - Children with intrinsic causes
    - Echogenic and slightly enlarged kidneys
  - Bilateral hydronephrosis or hydroureteronephrosis and bladder wall thickening indicate obstruction of bladder outlet causing postrenal oliguria/anuria.
  - Ultrasonography can detect congenital disorders, such as polycystic kidney disease and multicystic dysplastic kidney.
- Doppler examination of renal blood flow is helpful in diagnosing renal vascular thrombosis.

CLASSIFICATION

- Prerenal: Dehydration is the most common cause of oliguria/anuria in children.
- Renal: intrinsic renal disorders, such as acute tubular necrosis and glomerulopathies.
- Postrenal: obstruction to urinary flow in posterior urethral valves in boys.

TREATMENT APPROACH

- Major goal of treatment of prerenal oliguria/anuria is to restore intravascular volume.
- Oliguria/anuria due to intrinsic renal conditions needs to be managed by a pediatric nephrologist.
- Management of oliguria also includes timely treatment of underlying etiology.
- Urology needs to be consulted in patients with postrenal obstructive lesions.

SPECIFIC TREATMENTS

- A dehydrated child with oliguria/anuria should receive a fluid bolus of physiologic (normal) saline or lactated Ringer solution at 20 mL/kg to restore fluid volume.
  - Depending on response, another bolus may be needed.
- Estimation of volume status is needed to begin and continue fluid therapy.

- Amount is assessed by history and physical examination that includes assessment of
  - Body weight
  - Anterior fontanel in infants
  - Heart rate
  - Mucous membranes
  - Skin turgor
  - Capillary refill
  - Peripheral edema
  - Blood pressure
- Children with oliguria and volume overload may
  - Benefit from furosemide
  - Require fluid restriction
  - Need blood pressure and acid-base monitoring
- Children with oliguria due to obstruction may require urinary catheterization.
  - Relief of obstruction may be followed by post-obstructive diuresis and may need fluid/electrolyte replacement.

WHEN TO ADMIT

- See When to Refer section.

WHEN TO REFER

- Refer to a nephrologist or admit (or both) if child has any of the following symptoms:
  - Persistent oliguria or anuria despite adequate fluid challenge in a dehydrated child
  - Persistent oliguria or anuria that continues after removal of the offending nephrotoxins
  - Oliguria or anuria associated with
    - Swelling
    - Hypertension
    - Gross hematuria
    - Abnormal blood chemistry
    - Severe systemic signs or symptoms
  - Urology referral for oliguria or anuria caused by obstructive uropathy

PREVENTION

- The key to preventing oliguria or anuria is adequate hydration in at-risk patients.
  - Patients who have just undergone surgery
  - Patients receiving nephrotoxic medications
    - Amphotericin B
    - Acyclovir
    - Radiocontrast agent
  - Patients at risk of tumor lysis syndrome
  - Patients at risk of pigment nephropathy caused by hemoglobinuria or myoglobinuria

Anxiety

DEFINITION

- Generalized anxiety disorder
  - Excessive anxiety and worry, usually about school performance, events, or activities
- Panic disorder
  - Recurrent, unexpected, abrupt surge of intense fear or discomfort that reaches a peak within minutes
  - Sweating, trembling, palpitations, dizziness
- Separation anxiety disorder
  - Developmentally inappropriate and excessive fear or anxiety concerning separation from those to whom the individual is attached
- Agoraphobia
  - Marked fear or anxiety in
    - Using public transportation
    - Being in open or enclosed spaces
    - Standing in line or being in a crowd
    - Being outside of the home alone
- Social phobia
  - Marked fear or anxiety about social situations with exposure to possible scrutiny by others
  - In children, must occur in peer settings and not just with adults
- Specific phobias
  - Marked fear or anxiety about a specific object or situation (eg, insects, heights, storms, needles, airplanes, loud sounds, costumed characters)
  - In children, may be expressed by crying, tantrums, freezing, or clinging
- Obsessive-compulsive disorder (OCD)
  - Obsessions: recurrent and persistent intrusive and unwanted thoughts, urges, or images
  - Compulsions: repetitive behaviors or mental acts that an individual is driven to perform, often in response to an obsession or rigidly applied rules
- Posttraumatic stress disorder (PTSD)
  - Development of characteristic symptoms following exposure to actual or threatened death, serious injury, or sexual violence

HISTORY

General

- Children's fears may
  - Be developmentally normal.
  - Be exaggerated or persistent beyond norms for their age.
  - Result in reactions or panic attacks that impair function at school, at home, or with peers.
- Symptoms and findings (**Box 1**) may be elicited from parents or youth.
- Parents and youth often disagree on the severity of symptoms.
  - Agreement is much better if the discussion is about whether there are symptoms at all.

Assessment Plan

- Differentiate the child's symptoms from typical behavior.
  - Avoid misinterpretation in children who have a temperament marked by difficulty with change and wariness of new situations or individuals.
- Some stages in which particular anxieties normally emerge include
  - 8–9 months
    - Peak of stranger anxiety
  - Toddlers and early school age
    - Separation anxiety (fear of new people, places, or being away from trusted caregivers).
      - Usually ending by age 2–3 years
    - Intolerance of changes to routine or of novel experiences (seen in varying degrees in individuals).
    - Fear of the dark is common and exacerbated by other stresses or exposure to frightening media.
  - 5–8 years
    - Increased worry about harm to parents or attachment figures, possibly triggered by
      - Illness or death in family members
      - Child's own illness
      - World events
  - School-aged children of any age
    - Anxiety and distress over high-stakes testing
    - Initial reluctance to socialize in new situations
  - Adolescence
    - Previously resolved anxieties often recur in early adolescence.
    - Sometimes associated with appearance, social situations, or school performance.
- Verbal older children and adolescents can usually describe their fears ("worries" may be a more understandable concept).
- Evaluating a younger child's anxiety may be challenging, especially if the parent is anxious.
- Communicate directly with children about fears and physiologic symptoms.
- Depression or bereavement may mimic or co-occur with anxiety, so explore other emotional symptoms and current stressors.
- When children and youth of any age are anxious, ask about stressors in the family environment.

Box 1. Symptoms and Clinical Findings Suggesting Anxiety

Normal fears (eg, strangers, dark, separation, new social situations, unfamiliar animals or objects, public speaking) are exaggerated or persistent.

Fears are keeping child from developmentally appropriate experiences (eg, school refusal, extreme shyness or clinging, refusal to sleep alone).

Tantrum, tearfulness, acting-out behavior, or another display of distress occurs when the child is asked to engage in feared activity.

Child worries about harm coming to self or loved ones or fears something bad is going to happen.

Behavior changes following a traumatic experience, such as abuse, witness to violence, loss of a loved one, or medical trauma, as follows:

- **Infants and toddlers:** crying, clinging, change in sleep or eating habits, regression to earlier behavior (eg, bed-wetting, thumb-sucking), repetitive play or talk
- **3- to 5-year-olds:** separation fears, clinging, tantrums, fighting, crying, withdrawal, regression to earlier behavior (eg, bed-wetting, thumb-sucking), sleep difficulty
- **6- to 9-year-olds:** anger, fighting, bullying, irritability, fluctuating moods, fear of separation or of being alone, fear that traumatic events will recur, withdrawal, regression to earlier behavior, physical symptoms (eg, stomachaches, headaches), school problems (eg, avoidance, academic difficulty, difficulty concentrating)
- **10- to 12-year-olds:** crying, aggression, irritability, bullying, resentment, sadness, social withdrawal, fears that traumatic events will recur, suppressed emotions or avoidance of situations or discussions that evoke memories of the traumatic event, sleep disturbance, concern about physical health of self or others, academic problems or decline related to lack of attention
- **13- to 18-year-olds:** numbing, reexperiencing, avoidance of feelings (or situations or discussions that evoke memories of the traumatic event), resentment, loss of trust or optimism about future, depression, withdrawal, mood swings, irritability, anxiety, anger, exaggerated euphoria, acting out, substance use, fear of similar events, appetite and sleep changes, physical symptoms, academic decline, school refusal

Somatic features accompany worries: palpitations, stomachaches, headaches, breathlessness, difficulty getting to sleep, nausea, feeling wobbly ("jelly legs"), butterflies.

Panic attacks occur in response to feared objects or situations or happen spontaneously. These are unexpected and repeated periods of intense fear, dread, or discomfort along with symptoms such as racing heartbeat, shortness of breath, dizziness, light-headedness, feeling smothered, trembling, sense of unreality, or fear of dying, losing control, or losing one's mind. Panic attacks often develop without warning and last minutes to hours.

  - Serious illness (including anxiety and depression) in a family member
  - Economic problems
  - Marital discord
- Anxiety also may occur in multiple family members.
  - Helping parents manage their own anxiety can be very important, especially when using modeling as a form of treatment.

Panic Attacks

- Episodes of autonomic arousal that occur suddenly, often (but not always) cued by thoughts of a feared situation.
- Sudden onset of
  - Shortness of breath
  - Palpitations
  - Trembling
  - Diaphoresis
  - Feeling of faintness, dread, or impending doom
- Symptoms subside by themselves over the course of several minutes.
- Especially among teenagers, can be prolonged and result in a call for emergency medical assistance.
- Often improve as other aspects of anxiety are treated.

A

OCD

- Consider in the presence of marked rituals or compulsive behaviors.
- Normal phases of ritualized behavior usually can be distinguished from OCD by degree of distress caused by interruption of ritual.
- Individuals with OCD usually report that
  - Symptoms have a major effect on how they plan activities or interact with others.
  - Attempts to stop the thoughts or actions are difficult to carry out or even contemplate.
  - School-aged children and adolescents often admit to being aware that there is something objectively out of proportion about their concerns.
- Common concerns include
  - Contamination—fear of touching things that may be dirty, or the need to repetitively wash or bathe
  - Need to check that something has been done (usually related to security—doors locked, stove turned off)
  - Need to have one's personal possessions in a particular order or place

PTSD

- Consider if the onset of anxiety was preceded by an extremely distressing experience.
  - Witnessing violence
  - Losing a loved one
  - Undergoing medical trauma
  - Experiencing sexual or physical abuse
- Triggering circumstances need only be traumatic in the eye of the child.
- Clinicians may need to interview children and parents separately to elicit a complete history.
  - Parents may be unaware of trauma such as bullying at school or in the community.
  - Major traumas in the family (eg, serious illness in a parent) that are not discussed or disclosed.
- Hallmark symptoms of anxiety in the wake of trauma include
  - Reexperiencing (often repetitive play in young children)
  - Avoidance of memories or situations that recall the trauma
    - Changing the subject or acting inappropriately when trauma-related subjects are brought up in conversation
  - Hypervigilance (eg, increased worry about safety, startling or anxiousness at unexpected sounds or events)
- Children most at risk for PTSD following trauma or loss include those with
  - Preexisting mental health conditions
  - Caregivers experiencing emotional difficulties
  - Preexisting or consequent family life stressors
  - Previous loss or trauma
  - Repeated exposure to media coverage of traumatic events
  - Limited support network
- Provide the child with a safe and comfortable environment to express her feelings; allow the child to control the interview, take breaks, or discontinue as needed.

PHYSICAL EXAMINATION

- Standardized psychosocial screening instruments may be used (**Table 1**).
- Additional instruments can help confirm findings of initial screenings.
  - Spence Children's Anxiety Scale
  - Screen for Child Anxiety Related Disorders 2 (SCARED)
- Functional assessment tools help determine whether child is significantly impaired by symptoms.
  - Strengths and Difficulties Questionnaire (SDQ)
  - Columbia Impairment Scale (CIS)
- Tools to assess the effect of the child's problem on other members of the family.
  - Caregiver Strain Questionnaire (CGSQ)
- Differentiate the use of these tools as screening instruments at routine visits from use to refine concerns that have already been raised.
  - As screening tools, they tend to have relatively low sensitivity and positive predictive value.
  - Positive results need further discussion, and negative results may not be reassuring if parent or child is truly concerned.
  - When used to follow up on existing concerns, results still need discussion with families but are more likely to be a fair indicator of the nature and severity of problems.

DIFFERENTIAL DIAGNOSIS

- Learning problems or disabilities
- Somatic symptoms
  - Such as gastrointestinal symptoms, headaches, chest pain.
  - May elicit medical workups if they are not recognized as symptoms of anxiety.
  - Acute or chronic medical conditions or pain syndromes may cause anxiety.

Table 1. General Psychosocial Screening/Results Suggesting Anxiety

Screening Instrument	Score Suggesting Anxiety
Pediatric Symptom Checklist (PSC-35) (35 items)	• Total score ≥24 for age ≤5 years • ≥28 for age 6–16 years • ≥30 for age ≥17 years AND • Further discussion of items related to anxiety confirms a concern in that area.
PSC-17 (17 items)	• Internalizing subscale is ≥5. AND • Further discussion of items related to anxiety confirms a concern in that area.
Strengths and Difficulties Questionnaire (SDQ)	• Total symptom score of >19 • Emotional symptom score of 7–10 (See instructions at www.sdqinfo.com.) • Impact scale score of 1 (medium impairment) or ≥2 (high impairment) AND • Further discussion of items related to anxiety confirms a concern in that area.

- Depression
  - Coexists in half or more of anxious children
  - Symptoms
    - Marked sleep disturbance
    - Disturbed appetite
    - Low mood
    - Tearfulness without direct anxiety provocation
- Bereavement
  - Losses other than death of family members are traumatic and may trigger grief responses.
    - Separation or divorce of parents
    - Relocation
    - Change of school
    - Deployment of a parent in military service
    - Breakup with a girlfriend or boyfriend
    - Remarriage of a parent
  - May result in feelings of insecurity and anxiety immediately following the loss or exacerbate existing anxiety.
  - May make the child more susceptible to impaired functioning with subsequent losses.
- Autism spectrum disorder (pervasive development disorder and Asperger syndrome)
  - Also marked by problems with
    - Social relatedness (eg, poor eye contact, preference for solitary activities)
    - Language (often stilted)
    - Range of interest (persistent and intense interest in a particular activity or subject)
    - Rigid expectations for routine or parent promises
    - Anxiousness or anger if these expectations are not met
- Exposure to adverse childhood experiences
  - Determination of temporal relationship between the trauma and onset of anxiety symptoms is essential.
  - Denial of symptoms does not mean trauma did not occur.
  - Repeat questions about adverse childhood experiences as a trusting relationship is established.
- Psychosis
  - Symptoms associated with psychosis, such as hallucinations or delusions, may occur in children with PTSD.

- Symptoms may occur infrequently with adolescent onset of bipolar disorder.
- Symptoms are features of schizophrenia, which may have its onset in adolescence.
- Teens may manifest fear without disclosing hallucinations or delusions.

- Physical illness
  - Medical issues can mimic or provoke anxiety symptoms.
    - Thyroid disease
    - Hypoglycemia, asthma exacerbations, cardiac conditions
    - Side effects of medications (eg, bronchodilators)
    - Endocrine tumors (pheochromocytoma)
  - Drug or alcohol withdrawal is a consideration for teens (potentially a medical emergency).
- Selective mutism
  - Consider if a child who has had normal language development suddenly stops talking in certain situations (most often in school and to adults outside the home).
  - Can be confused with children making a language transition (eg, a child raised speaking Spanish who is suddenly placed in an English-speaking class).

TREATMENT APPROACH

- Anxiety
  - Identify specific situations that trigger anxiety.
  - Help individuals learn how to reduce anxious feelings and gradually become tolerant of triggers.
  - Tailor approaches to the specific triggering situation.
    - Carefully support increasing exposure.
    - Practice of cognitive, somatic, and social coping strategies.
- OCD and PTSD
  - Same treatment elements as for anxiety; however, cause of the disorder takes on a role in treatment.
  - OCD
    - Important for child and family to understand that obsessions and compulsions develop without particular triggers (though they can be worsened by other stresses)
  - PTSD
    - Linking nonspecific symptoms to a past trauma can be an important part of treatment.
- Care of a child with anxiety can begin in the primary care setting from the time symptoms are recognized, regardless of whether referral to a mental health specialist is ultimately part of the care plan.
- Helping parents appreciate their own areas of comfort and discomfort, and how these may differ from those of their child, can be a first step toward treatment.
- Parents can be guided to learn ways to help their child gain better emotional regulation.

SPECIFIC TREATMENT

- Engage child and family in care.
  - Process may require multiple primary care visits.
  - Reinforce strengths of the child and family.
    - Good relationships with at least one parent or important adult
    - Prosocial peers
    - Concerned or caring family
    - Help seeking
    - Connection to positive organizations
  - Identify any barriers (eg, stigma, family conflict, resistance to treatment).
  - Use "common factors" techniques to build a therapeutic alliance with the child and family (**Box 2**).
  - It is normal for people with anxiety to initially resist treatment.
    - Most people cope with anxiety through avoidance.
- Provide psychoeducation.
  - Explain to the family that anxiety is a normal, common human emotion that can be addressed.
  - Acknowledge that variations in temperament or style make some people more or less anxious with new situations or threats.
  - Inform patients that anxiety has nothing to do with bravery or accomplishment.
  - Point out that one can very much enjoy and be good at things but still experience anxiety in front of others or in high-stakes circumstances.
- Encourage healthy habits.
  - Exercise
  - Outdoor play
  - Balanced and consistent diet
  - Sleep (critically important to mental health)
  - Special time with parents
  - Frequent acknowledgment of the child's strengths
  - Open communication with a trusted adult about worries

Box 2. HELP Build a Therapeutic Alliance

H = Hope

Increase the family's hopefulness by describing your realistic expectations for improvement and reinforcing the strengths and assets you see in the child and family.

E = Empathy

Communicate empathy by listening attentively.

L^2 = Language, Loyalty

Use the child or family's own language to reflect your understanding of the problem as they see it and to give the child and family an opportunity to correct any misperceptions.

Communicate loyalty to the family by expressing your support and your commitment to help.

P^3 = Permission, Partnership, Plan

Ask the family's permission for you to ask more in-depth questions or make suggestions for further evaluation or management.

Partner with the child and family to identify any barriers or resistance to addressing the problem, find strategies to bypass or overcome barriers, and find agreement on achievable steps aligned with the family's motivation.

Establish a plan (or incremental first step) through which the child and family will take some action(s), work toward greater readiness to take action, or monitor the problem, then follow up with you, based on the child and family's preferences and sense of urgency. (The plan might include, for example, gathering information from other sources such as the child's school, making lifestyle changes, applying parenting strategies or self-management techniques, reviewing educational resources about the problem or condition, initiating specific treatment, seeking referral for further assessment or treatment, or returning for further family discussion.)

From American Academy of Pediatrics. *Addressing Mental Health Concerns in Primary Care: A Clinician's Toolkit* [CD-ROM]. Elk Grove Village, IL: American Academy of Pediatrics; 2010.

- Shielding young children from disturbing media

■ Reduce stress.
- Consider the child's social environment.
  - — Family social history
  - — Parental depression
  - — Results of family assessment tools
  - — Reports from child care or school
- Raise the following questions:
  - — Is an external problem causing the child to be anxious?
    - ■ Take steps to address the problem.
  - — Is the child exposed to frightening electronic media?
    - ■ May result from unsupervised access to television or Internet content.
    - ■ May occur during shared family activities when family members underestimate or fail to recognize the child is frightened.
    - ■ Limit these exposures; provide reassuring explanations if they occur.
  - — Is the child's worry about a parent's welfare legitimate because of a serious illness, domestic violence, or parent impairment?
    - ■ Address environmental issues.
    - ■ Enlist the help of school personnel or social services as appropriate.
  - — Is the parent anxious, depressed, or impaired because of a substance use disorder? Has the parent experienced trauma or loss?
    - ■ Advise parents to minimize their own displays of fear or worry when the child is present.
    - ■ Consider referral to adult mental health services.

■ Offer initial psychosocial intervention(s) to address the anxiety symptoms (**Table 2**).
- Apply to children with mild or emerging anxiety symptoms and those with impairing symptoms not at the level of a disorder.
- A carefully administered psychosocial treatment plan may be a reasonable first step until severity and natural history of the anxiety are better understood.

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Table 2. Psychosocial and Psychopharmacologic Treatments for Anxiety

Psychosocial Treatments (as of April 2017)		
Problem Area	**Level 1—Best Support**	**Level 2—Good Support**
Anxious or avoidant behaviors	• Cognitive behavior therapy (CBT) • CBT and medication • CBT for child and parent • Education • Exposure • Modeling	• Assertiveness training • Attention • Attention training • CBT and parent management training • CBT with parents only • CBT and music therapy • Cultural storytelling • Family psychoeducation • Hypnosis • Relaxation • Stress inoculation
Traumatic stress	• CBT • CBT with parents • Exposure • Eye movement desensitization and reprocessing	• None
US Food and Drug Administration–Approved Psychopharmacologic Interventions		
Diagnostic Area	**Psychopharmacologic Intervention**	
Anxiety disorders	• The only psychopharmacologic interventions approved by the US Food and Drug Administration are selective serotonin reuptake inhibitors (sertraline, fluvoxamine) and clomipramine for the treatment of obsessive-compulsive disorder. • No psychopharmacologic interventions have been approved for other anxiety disorders, although several randomly controlled clinical trials suggest their efficacy and safety.	

PracticeWise. Evidence-Based Child and Adolescent Psychosocial Interventions. https://www.aap.org/en-us/Documents/CRPsychosocialInterventions.pdf. Accessed April 4, 2017.

For US Food and Drug Administration–approved interventions, go to www.fda.gov/ScienceResearch/SpecialTopics/PediatricTherapeuticsResearch/default.htm.

- Interventions can be used as initial primary care management and while readying children for referral or awaiting access to specialty care.

■ Guide parents in managing the child's fears.
- Help parents identify their child's fear(s) and reach consensus on the goal and means of reducing symptoms.
- Teach the child and parent cognitive behavioral strategies to improve coping skills.
  - — Deep breathing
  - — Muscle relaxation
  - — Positive self-talk
  - — Thought stopping
  - — Thinking of a safe place
- Child and family may benefit from reading material or a Web course.

■ Gradually increase exposure to feared objects or experiences.
- Goal is mastery rather than avoidance.
- Parent might start out with brief exposure to the

feared object or activity and gradually lengthen the exposure.
- Help the child imagine, discuss, and look at pictures about the feared object or activity.
- Teach child to tolerate a short exposure with support from the parent.
- Proceed to tolerate a longer exposure in a group or with the parent or coach.
- Tolerate the feared activity alone (when appropriate) but with a chance to get help.
- During these trials, parents need to remain calm and confident.

- Manage school phobia.
  - For some children, it is necessary to return the child promptly to the anxiety-producing situation.
  - Rule out bullying, trauma, learning difficulties, and medical conditions.
  - Partner with school personnel to manage the child's return to school and insist that the child attend school, while providing positive feedback and calm support.
  - If absence becomes prolonged or parents are reluctant to support the child's return, referral to a mental health specialist will be necessary.
- If anxiety is secondary to environmental stress, support the parents' efforts to protect the child, buffer stress, and help the child master his anxiety.
  - Help the child to rename the fear (ie, "annoying worry") and assist the child to become the boss of the worry.
  - Reward brave behavior (**Table 3**).
- Attend to overall parenting style.
  - Children can become anxious if parents are inconsistent about rules and expectations.
  - Determine whether there are catastrophic consequences for failure.
  - Explore the child's sense of responsibility for the family's stresses.
- Treat panic attacks.
  - Early treatment may prevent progression to agoraphobia, depression, or substance use disorder.
  - Awareness of triggers for attacks and development of alternative responses can diminish the frequency of attacks.
  - For attacks that appear without apparent triggers, referral for pharmacologic treatment may be most effective (see **Table 2**).
- Medication
  - Can be helpful in suppressing panic and OCD symptoms or treating time-limited and severe stressors.
  - In the absence of psychosocial treatments, symptoms may recur as the medications are discontinued.
  - Interpreting results of a medication trial can be problematic, as the severity of anxiety problems is often cyclic.
  - Families may seek care as symptoms are peaking; if medication is started at this point, it may be unclear if the condition improved on its own or responded to medication.

WHEN TO REFER

- Involve specialists if the child does not respond to initial interventions or if the following clinical circumstances exist:
  - Child has severe functional impairments at school, at home, or with peers (eg, if anxiety threatens to interfere with academic progress or other developmentally important goals).
  - Multiple symptoms of anxiety occur in many domains of life (eg, fearful of new situations, reluctant to do things in public, trouble separating, worries a lot).
  - The child or parent is very distressed by the symptom(s).
  - There are co-occurring behavior problems.
  - The combination of shyness, anxiety, and behavior problems is particularly risky for future behavior problems of a more serious nature.
  - The anxiety was preceded by serious trauma or symptoms suggesting PTSD.
  - The child seems to have panic disorder or OCD, both of which require specialized treatment.
  - The anxiety occurs in a child with autism spectrum disorder.
    - Anxiety about normal childhood issues (eg, weather, animals), as well as the orderliness and predictability of daily routines, is relatively common among higher functioning children with autism spectrum symptoms, including stereotyped interests and poor social perceptions and skills.
- When specialty care is needed, ensure that it is evidence informed and assist the family in accessing it.
  - Various evidence-based and evidence-

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Table 3. Tips for Reward System

Reward Systems for Brave Behavior	Guidelines for Use
Small rewards	Include positive feedback.
Star charts	• Focus on only 1 or 2 behaviors at a time. • Have one star chart per behavior. • Negotiate rules for the star chart (eg, sleeping in own bed for 1 night = 1 star; 4 stars = trip to the pool). • Ignore mistakes and failures; do not even mark them on the star chart. • Continue awarding stars when they are earned.

informed psychosocial interventions, and some pharmacologic interventions, are available to treat anxiety disorders in children and adolescents.
- Ideally, those referred for care in the mental health specialty system would have access to the safest and most effective treatments.
- Youth referred for mental health specialty care complete the referral process only 61% of the time, and significantly fewer persist in care.
- Approaches to improving the referral process include making sure that the family
  - Is ready for this step in care
  - Has some idea of what the specialty care will involve
  - Understands what the primary care physician's ongoing role may be
- If the specialty appointment is not likely to occur soon, the physician can work with the family on a plan to manage the problem as well as possible in the meantime.
- Not all evidence-based interventions may be available in every community.
- If a particular intervention is not available, this becomes an opportunity to collaborate with others in the community to advocate on behalf of children.
- Increasingly, states offer tele-psychiatry services and consultation or referral support "warm lines" that help physicians provide initial treatment and locate resources.
- The availability of the latter form of help is tracked at www.nncpap.org.

■ Reach agreement on respective roles in the child's care.
- If the child is referred to mental health specialty care for an anxiety disorder, the physician may be responsible for
  - Initiating medication or adjusting doses
  - Monitoring response to treatment
  - Monitoring adverse effects
  - Engaging and encouraging the child's and family's positive view of treatment
  - Coordinating care provided by parents, school, medical home, and specialists
- The child may improve just knowing that the physician is involved and interested.

FOLLOW-UP

■ Provide resources.
- Provide the family with contact numbers and resources in case of emergency.

■ Monitor the child's progress toward therapeutic goals.
- Screening instruments with multiple reporters (youth, parent, teacher) can help in monitoring progress.

PROGNOSIS

■ Counsel family that it is not uncommon for treatment to be successful for a period and then seem to lose effectiveness.
- Caused by new stresses or demands or by a letup on treatment.
- If troubleshooting existing treatment and ways of dealing with new stresses does not help get function back to baseline, consider new treatments or new diagnoses.
- As school demands increase, learning issues may need to be considered even if they were not seen as contributors in the past.

DEFINITION

- An apparent life-threatening event (ALTE) is
  - Frightening to the observer, who may fear the newborn or infant has died
  - Characterized by some combination of
    - Apnea
    - Color change
    - Marked change in muscle tone
    - Choking
    - Gagging
- ALTE was intended to replace the terms
  - Aborted crib death.
  - Near-miss sudden infant death syndrome (SIDS).
  - Change corrects erroneous implication of an association between ALTE and SIDS.
- ALTE is not a diagnosis but, rather, a reflection of a symptom constellation ("chief complaint") that requires evaluation to determine an etiology to guide risk assessment and subsequent therapeutic response.
- Pathologic apnea
  - Respiratory pause
    - Prolonged, lasting ≥20 seconds *or*
    - Associated with cyanosis, pallor, hypotonia, or bradycardia
  - Central apnea (CA)
    - Total cessation of inspiratory efforts with no evidence of obstruction.
    - Cessation of breathing during sleep without any breathing effort for ≥20 seconds *or*
    - Lasting at least 2 breaths' duration with 3% oxygen desaturation or arousal.
    - In infants, CA is at least 2 breaths in duration and is associated with a decrease in heart rate to <50 beats per minute for at least 5 seconds, or <60 beats per minute for 15 seconds.
  - Obstructive apnea
    - Infant tries to breathe against an obstructed upper airway, resulting in chest wall motion without airflow throughout the apneic episode.
  - Mixed apnea
    - Obstructed respiratory efforts, usually following central pauses
- Periodic breathing (common in neonates and young infants)
  - Breathing pattern
    - ≥3 respiratory pauses >3 seconds
    - <20 seconds of respiration between pauses
  - Pauses in breathing without any physiologic consequences also occur in preterm and term newborns.

SIGNS AND SYMPTOMS

History

- Detailed history and description of the neonate or infant at the time of the ALTE
  - Most infants appear normal by the time of evaluation.
  - Most important objective is to determine, if possible, whether an "event" actually occurred.
  - If a reliable observer reports a seemingly frightening event, the infant should be hospitalized to determine if a cause can be found.
  - If the observer is unreliable, and the history equivocal, the infant might be discharged from the emergency department (ED).
  - If the history is equivocal, the best choice may be to hospitalize and evaluate, especially when a pediatrician might not be available in the ED.
  - Consistency of the described event should be evaluated because fabricated events may suggest child abuse.

Essential Elements in the History of ALTEs[1]

- Personal and family history
  - Perinatal history
    - Full-term or preterm birth
    - Pregnancy or perinatal complications
  - Medical and surgical history
    - Previous evaluations and treatments
    - Prior hospitalizations
    - Medications
  - Feeding habits
    - Breastfeeding or bottle-feeding
    - Usual amount and frequency of feedings
    - Timing of last feeding relative to event
    - Feeding difficulties—choking, coughing, arching, grimacing, emesis/reflux
    - Usual behavior and temperament
  - Breathing and sleep history
    - Sleep patterns
    - Breathing irregularities, respiratory pauses or shallow breathing
    - Episodes of cyanosis, pallor
  - Family history
    - Siblings with ALTE, SIDS, or early death
    - Family history of genetic, metabolic, cardiac, or neurologic problems
  - Parental or caregiver history
    - Smoking or drinking habits
    - Recent medical problems and treatments

- Daily life conditions
  - Usual sleep conditions
    - Position when placed down for sleep and when found
    - Sleep location
    - Sleeping attire
    - Bedding materials
  - Other conditions
    - Clothing, accessories (eg, necklace, bracelet)
    - Room temperature, over-bundling
    - Use of pacifiers
  - Brief CAs following body movements and periodic breathing ("physiologic" CAs)
    - Common in healthy newborns and infants during the first months of life.
    - Duration and frequency improves with age.
    - Those lasting >15 seconds reflect developmental immaturity and rarely persist after 3 months of age.
    - Most apneas occur during rapid eye movement sleep or as the newborn or infant is transitioning between sleep states.

Circumstances and Characteristics of ALTE

- Events immediately preceding ALTE
  - Recent fever or illness
  - Medications for the newborn or infant and others in the home
  - Immunizations
  - Sleep deprivation
  - Change in daily life routine
- Description of ALTE
  - Place and time
    - Exact place in which the ALTE occurred
      - Infant's bed
      - Parent's bed
      - Parent's arms
      - Bathroom
      - Sofa
      - Car
    - Time of event
    - Time since last feeding
    - Estimated time to recover from ALTE
    - Estimated duration of event
  - Witnesses and interventions
    - Who discovered or witnessed the ALTE
    - What led to the discovery of the ALTE (eg, noise, unusual cry)
    - Interventions performed
      - Gentle stimulation
      - Shaking
      - Cardiopulmonary resuscitation (CPR)
    - Infant's response to the intervention
  - Description of infant during ALTE
    - State of infant when event began: asleep or awake
    - If asleep
      - Body position
      - Type of bedding
      - Face covered or free
    - If awake, was the infant
      - Being fed
      - Being handled
      - Crying
      - Being bathed
    - Infant's appearance when found
      - Consciousness
      - Muscle tone
      - Color
      - Respiratory effort
        - Choking
        - Gasping
      - Emesis
      - Sweating
      - Limb or eye movements
      - Pupil size
      - Skin or rectal temperature
- A complete history should include
  - Review of the patient's and family history
  - Description of the patient's living conditions
  - Descriptions of events immediately before and during the ALTE
  - History or family history of SIDS or ALTEs
- All patients should be screened for risk factors for child abuse.

Physical Examination

- Detailed physical examination is essential to uncover clues to the underlying cause.
- The pediatrician should
  - Pay particular attention to abnormalities that may account for the infant's symptoms.
    - Neurologic
    - Respiratory
    - Cardiac
  - Note evidence of physiologic compromise.
    - Mental status changes
    - Cyanosis
    - Apnea
- Note physical examination features for child abuse: unexplained bruising, bleeding, or petechiae of the face.
- Physical findings of trauma should be well described in the chart and should include photographs labeled with the infant's name and birth date.

DIFFERENTIAL DIAGNOSIS

- Differential diagnosis focuses on determining the underlying condition associated with the ALTE.
- Gastrointestinal
  - Gastroesophageal reflux disease (GERD) (31%)
    - Diagnosis most often associated with an ALTE.
    - Definite causal relationship not demonstrated, but one study suggested that spontaneous respiratory events occurred more often in ALTE infants and that respiratory inhibition may be exaggerated during pharyngeal swallowing events.
- Neurologic
  - Seizures (11%)
- Respiratory
  - Lower respiratory tract infections (8%)
    - Pertussis
    - Respiratory syncytial virus infection
- Cardiovascular
  - Cardiac arrhythmias
  - Persistent ductus arteriosus
- Endocrine, metabolic
  - Inborn errors of metabolism
- Infectious
  - Urinary tract infections
- Neoplastic
  - Brain tumor
- Drug related
  - Opioid-related apnea
- SIDS
  - Apnea is not predictive of nor a precursor to SIDS.
    - ALTEs are not near-miss SIDS cases.
    - Apnea appears to resolve at an age before most SIDS deaths occur.
  - Infants with an ALTE are
    - 1–3 months younger than infants who die of SIDS
    - More likely to be found during the daytime or while sleeping supine at the time of the event
  - <7% of patients with SIDS have a history of an ALTE.
  - Although the SIDS mortality rate markedly decreased between 1986 and 1994, the mean annual admission rate for ALTEs did not change significantly.
  - Despite the lack of an epidemiologic association between SIDS and ALTEs, a very small minority of ALTEs go on to have SIDS and a small minority of SIDS deaths had a preceding ALTE.
- Sudden unexpected postnatal collapse (SUPC)
  - Reported survival rates vary from 50%–80%.
  - Rare but well-described event that includes severe ALTE and sudden infant death occurring during the first week of life in newborns in whom postnatal adaptation seems normal.
  - Estimated incidence of an SUPC in a presumably healthy newborn ranges from 2.6–133 cases/100,000.
  - Reported SUPC typically excludes
    - Newborns with known risks for ALTE and SIDS
    - Newborns born at <35 weeks' gestation or with diagnosed congenital malformations
    - Newborns who experience perinatal asphyxia
  - When a defined time for the SUPC event is described, approximately one-third of reported events occur, respectively,
    - During the first 2 hours after birth
      - Most reported events that occur ≤2 hours of birth have been during skin-to-skin contact and the first breastfeeding attempt.
    - Between 2 and 24 hours after birth
    - Between 1 and 7 days after birth
  - The transition from fetal to extrauterine life could make the newborn more vulnerable.
    - The initial surge of adenosine, prostaglandins, and catecholamines during and after birth is followed by a period of diminished responsiveness to external stimuli and increased vagal tone.
  - Contributing factors
    - Prone positioning of the newborn placed in skin-to-skin care
    - Unsupervised breastfeeding during the first 2 hours
    - Primiparous mother
    - Parents left alone with newborn during first hours after birth
    - Distractions, such as smartphone use
    - Maternal fatigue and sedation following an exhausting labor
  - Newborns born late preterm and early term (37–38 weeks' gestation) comprise an important risk group.
  - Mothers may fail to recognize their newborn's deterioration because of inexperience and lack of awareness that the newborn is having difficulty.

- Signs such as a change in color or respiratory effort may be more difficult to observe if maternal mobility is impaired because of pain, postoperative status, or spinal anesthesia.
- Among survivors, half have neurologic sequelae.
- Among newborns who die and undergo post-mortem examination, underlying congenital anomalies and conditions have been described.
  - Antenatal brain injury
  - Infection
  - Metabolic defects
  - Congenital central hypoventilation syndrome
  - Congenital adrenal hypoplasia
  - Cardiac abnormalities such as structural anomalies, cardiomyopathy, infarction, and conduction
- Among newborns dying unexpectedly in the first week of life, almost 60% are explained following postmortem examination.
- All newborns who suffer a sudden and unexpected cardiorespiratory collapse within the first week of life should undergo comprehensive investigation to determine the underlying cause.
- If the newborn dies, a complete postmortem examination should be performed, including
  - Metabolic testing
  - Mitochondrial disease testing
  - Genetic testing
- This should be followed by a multidisciplinary investigation and case review that explores
  - Family, obstetric, pregnancy, delivery, and postnatal history
  - Health of the newborn until collapse
  - Postnatal transition and feeding
  - Circumstances surrounding collapse, and resuscitation

■ Other

- Child abuse (non-accidental trauma and suffocation) should be considered in infants with a history of
  - Recurrent cyanosis.
  - Apnea.
  - ALTE witnessed only by a single caregiver or in a family with previous unexplained infant deaths.
  - Clinicians must avoid stigmatizing or adding to the distress of families.
- Child abuse and factitious illness may account for 11% of unexplained ALTEs.
- All pediatricians and nonphysician clinicians should
  - Be trained to recognize the historical features and physical examination findings
  - Have a systematic approach to screen all ALTE patients for abuse
- When a death occurs in an infant with a prior history of ALTE, the following circumstances should indicate the possibility of intentional suffocation[2]:
  - Previous recurrent cyanosis, apnea, or ALTE while in the care of the same person
  - Age at death >6 months
  - Previous unexpected ALTE witnessed only by a single caregiver or in a family with previous unexplained infant death of ≥1 siblings
  - Simultaneous or nearly simultaneous death of twins
  - Previous death of infants under the care of the same unrelated person
  - Discovery of blood on the infant's nose or mouth in association with ALTEs

DIAGNOSTIC APPROACH

■ Most patients will be discharged from the ED or hospital without a specific diagnosis or with a self-limited condition not requiring treatment.

■ A minority might have one of many occult disorders that can lead to significant morbidity or mortality if unidentified.

■ No single accepted standard for evaluation.

- Thorough clinical assessment is most likely to lead to a diagnosis of the underlying problem.
- Diagnostic studies and observation should be based on the findings of the clinical assessment.
  - The increasing likelihood of false-positive results may diminish diagnostic value and unnecessarily increase risk for iatrogenic complications.

LABORATORY FINDINGS

■ The yield of most studies is low.

- Even if a positive result is found, the question of a causal relationship remains.

■ Consider the following studies in infants with no identified cause after clinical assessment:

- Complete blood cell count
- Basic metabolic panel and ammonia
- Urinalysis
- Blood culture
- Urine culture

- Additional studies to consider after an initial period of observation include
  - Metabolic studies
    - A pediatric specialist may need to be consulted to interpret the results.
  - Tests for respiratory pathogens as indicated
  - Toxicology screen
  - Liver function tests to screen for occult abdominal injury

IMAGING

- Consider in infants with no identified cause after clinical assessment and observation period.
  - Chest radiography
  - Skeletal survey
- Upper gastrointestinal series.
  - Not recommended for diagnosing GERD because reflux is present in most infants but may be used to identify conditions that contribute to GERD.
    - Volvulus
    - Gastric outlet obstruction
    - Tracheoesophageal fistula
    - Vascular rings
- Neuroimaging.
- Gastroesophageal reflux study.

DIAGNOSTIC PROCEDURES

- Electrocardiography
  - Consider in infants with no identified cause after clinical assessment.
- Continuous cardiorespiratory monitoring with pulse oximetry
  - Detects
    - Apnea
    - Bradycardia
    - Hypoxemia
  - Typical apnea settings of 20 seconds on a cardiorespiratory monitor may miss
    - Bradycardia
    - Clinically relevant respiratory pauses (<20 sec)
    - Obstructive and mixed apnea events that lead to hypoxemia
- Polysomnography (PSG)
  - Used most commonly to evaluate children for obstructive sleep apnea and cardiorespiratory function in infants and children with chronic lung disease or neuromuscular disease.
  - PSG requires hospitalization, typically overnight, although a 4-hour period of monitoring during sleep periods may be sufficient to identify central, obstructive, and mixed apneas.
  - May provide more detailed information about cardiopulmonary abnormalities during sleep and feeding.
  - If a pH probe is used, the relationship between the apneas and gastroesophageal reflux, if present, can be examined.
  - Routine PSG is unnecessary but may contribute to diagnosis when there is significant respiratory compromise, concern for CA, or anatomic abnormalities of the head and neck, or when there has been >1 ALTE.
  - If obstructive apnea is identified as a cause for an ALTE, repeat PSG may be necessary to determine when and if intervention is needed.
- Pneumography
  - 12- to 24-hour recording of breathing effort, heart rate, oxygen level, and airflow to the lungs during sleep.
  - Useful in identifying abnormal breathing patterns, with or without bradycardia, especially in preterm newborns and infants.
  - Less expensive; can be performed in the home or hospital setting.
  - Unattended studies that collect data on respiratory effort with
    - Thoracic impedance monitor
    - Nasal flow
    - Oxygenation
    - Cardiac rhythm
  - But not
    - Sleep staging
    - Carbon dioxide signal
    - Abdominal effort
  - Pneumography generates more technical artifacts and is less informative than PSG.
  - Should be limited to medical centers where PSG is unavailable.
  - Might detect CA events with oxygen desaturation or bradycardia and could confirm a relationship to acid reflux events if paired with a pH probe monitor.

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- 24-hour pH probe
  - If GERD is the suspected cause of an ALTE.
  - ≤89% of infants with an ALTE may have a positive result.
    - Only 41% of these have a correlating clinical diagnosis.
- Dilated funduscopic examination

TREATMENT APPROACH

- Simple observation is insufficient.
- A period of observation with continuous cardiorespiratory monitoring in the hospital when a benign cause of ALTE is not evident.
- Education and guidance should be provided to the guardian.
- Monitoring in the home setting after hospitalization detects recurrence.

SPECIFIC TREATMENTS

Hospital Admission

- Hospital admission may not be required if
  - The ALTE appears to be benign.
  - Patient is normal when evaluated immediately after the event.

Hospitalization With Cardiorespiratory Monitoring

- Required if
  - The episode was significant.
  - The newborn or infant required intense stimulation.
  - Physical examination reveals an abnormality.
  - The hospital environment may
    - Help document recurrent ALTEs.
    - Provide time for test results to return.
    - Reveal social concerns indicative of child abuse.

Intensive Care Unit Admission

- If the witnessed event or a review of the history suggests severe cardiorespiratory compromise
- Treatment directed at the underlying diagnosis
  - For example
    - Antibiotics for suspected bacterial infection
    - Anticonvulsants for an infant with seizures
    - Medications for GERD

WHEN TO ADMIT

- History of preterm birth.
- Witnessed apnea (central or obstructive) with oxygen desaturation or bradycardia by medical staff.
- Age <2 months or 48 weeks' post-menstrual age.
- Family history of SIDS.
- Suspected child abuse.
- Multiple ALTEs.
- Suspicion for central or obstructive apnea.
- There is no evidence to support routine hospitalization of all patients with ALTEs.
- The benefit to hospitalization must also be weighed against unintended consequences.
  - Increasing parental anxiety
  - Risk for nosocomial infections
  - Unnecessary testing or use of hospital resources
- The decision to hospitalize newborns or infants should be guided by initial assessment along with some special consideration for higher-risk groups (including presence of a responsible adult with CPR training in the home).
- Infants with post-menstrual age <44 weeks are a higher risk group, particularly if born preterm.

WHEN TO REFER

- When home CR monitoring is considered after a severe event requiring CPR.
- Suspected
  - Seizure disorder
  - Hypoxemia
  - Hypercarbia
  - Central, obstructive, or mixed apnea
  - Cardiac dysrhythmia
- Vascular ring identified.
- Congenital craniofacial anomalies with suspected obstructive apnea.
- Evidence of child abuse.
- Atypical manifestation.
- Documentation of apnea, bradycardia, and hypoxemia events in the hospital setting should warrant further evaluation and consultation with a pulmonary specialist.
- Assessments of suspected child abuse should be referred to child protective services and law enforcement.

FOLLOW-UP

- Home cardiorespiratory monitoring
  - Review of results by a pediatrician or specialist who is trained in their review.
  - Physician should establish a specific plan for periodic review.
    - In most cases, results should be reviewed monthly if the guardian has no concerns about the infant, or sooner if guardian reports ≥1 significant event.

- Discontinue when
  - No further physiologically significant events have occurred.
  - No further objective evidence of pathologic events for ≥6 weeks.
- Parents and caregivers should be counseled on
  - CPR for infants
  - Safe sleeping techniques (see Prevention section)

PROGNOSIS

- Morbidity and mortality vary according to underlying diagnosis.
  - Mortality of infants with apnea of infancy
    - 0%–6%
    - In healthy term and preterm infants, apnea events become rare by 43 weeks' postmenstrual age.
- ALTE recurrence rate
  - 0%–24%
- Long-term outcomes for infants with an unexplained ALTE
  - Unpredictable
  - Severe event requiring resuscitation, recurrent ALTE, or seizure disorder
    - >25% risk of death.
    - However, normal cognitive and behavioral outcomes have been reported up to 10 years after an ALTE.

PREVENTION

- Parents and caregivers should be counseled on
  - Safe sleeping tips.
  - Adults should avoid sleeping in same bed as newborns or infants because of the potential for accidental suffocation.
  - The safest place for a newborn or an infant to sleep is in a crib in the parents' room for the first 6 months of life.
- If the newborn or infant is going home on a monitor, all caregivers must be trained on how to respond to alarms.

REFERENCES

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Asthma

DEFINITION

- Asthma is a chronic inflammatory condition of the airways characterized by 3 features.
  - Airway obstruction that is at least partially reversible by bronchodilator treatment
  - Airway hyperreactivity or hyperresponsiveness to a variety of external stimuli
  - Chronic inflammation of the airway

SIGNS AND SYMPTOMS

- A detailed medical history should be obtained from the patient and family.
  - Nature and frequency of symptoms
  - Precipitating factors
  - Dyspnea with speech and with exertion
  - Response to medications
- To make the diagnosis of asthma, the pediatrician must determine whether
  - The child has recurrent episodic symptoms of airflow obstruction, such as cough, wheezing, shortness of breath, or chest tightness.
  - Airway flow obstruction or airflow limitation is at least partially reversible by administration of a bronchodilator.
    - In older children and adults, spirometry before and after bronchodilator use can serve as an ambulatory test of bronchial hyperresponsiveness.
    - In a younger child, a positive clinical response to an inhaled β-agonist may be useful to determine partial reversibility.
  - Ask about symptoms.
    - Intermittent and repetitive episodes of cough
    - Noisy breathing or wheezing triggered by respiratory infections, allergen or irritant exposure, exercise, or play
    - Frequency
    - Severity
    - Are the symptoms made worse by triggers?
      - Identify triggers, if possible.
    - Are the symptoms worse during the day or night?
    - Do symptoms wake the child?
  - In older children
    - Shortness of breath and chest tightness, particularly associated with physical activity
    - Nonspecific symptoms, including self-imposed limitation of physical activities, general fatigue, and difficulty keeping up with peers
    - Recurrent "croup" or frequent "clinical pneumonia" or "bronchitis"
- Physical examination should focus on the upper respiratory tract, chest, and skin.
  - Look for signs of allergic disease.
    - Eczematous skin
    - Erythematous conjunctiva with cobblestone
    - Allergic shiners
    - Morgan folds
    - Allergic salute
    - Pale boggy turbinates
    - Allergic nasal crease
    - Rhinorrhea
    - Polyps
  - Concomitant atopic features.
  - Characterization of breath sounds and measurement of the inspiration to expiration ratio may be of value.
- The chest examination may be unremarkable in children with asthma.
- The diagnosis of asthma in a child is often delayed or the severity underestimated.
  - Pediatricians commonly use labels for asthma, such as reactive airway disease, recurrent bronchitis, or wheezy bronchitis.
  - Use of this terminology may hinder appropriate diagnosis and therapy.
- Physical signs *not* usually associated with asthma include
  - Failure to thrive
  - Cyanosis
  - Clubbing

DIFFERENTIAL DIAGNOSIS

- Not all wheezes indicate asthma.
- Many of the following conditions may coexist with and exacerbate the severity of asthma:
  - Upper respiratory conditions
    - Allergic or chronic rhinosinusitis
    - Tonsillar or adenoidal hypertrophy
  - Middle respiratory tract conditions
    - Foreign body aspiration
    - Vocal cord dysfunction
    - Airway lesions such as airway stenosis, tracheal webs, or tracheomalacia and bronchomalacia
    - Vascular rings
    - Mediastinal masses
    - Vocal cord dysfunction or paralysis
  - Lower respiratory tract conditions
    - Viral bronchiolitis
    - Bronchiectasis
    - Primary ciliary dyskinesia (immotile cilia syndrome)

  - Hypersensitivity pneumonitis
  - Interstitial pneumonia
  - Bronchopulmonary aspergillosis
  - Pulmonary edema
  - Pulmonary eosinophilic disorders
  - Cystic fibrosis
    - Nasal polyps in a younger child may raise the suspicion of cystic fibrosis.
  - Pneumonia
  - Tuberculosis
  - Adverse effects of medications (eg, angiotensin-converting enzyme inhibitors)
- Gastroesophageal reflux or recurrent aspiration
- Cough variant asthma
  - Chronic cough alone may be a manifestation of asthma, especially in young children.
    - Diagnosed by monitoring of peak expiratory flow or methacholine inhalation challenge, if applicable.
    - Trial of bronchodilators may demonstrate reversibility.
    - If there is clinical improvement, treatment should follow the stepwise approach to long-term management of asthma.
  - Overdiagnosed as often as it is underdiagnosed.
  - If symptoms do not respond to traditional asthma therapies, alternate diagnoses include
    - Allergic rhinitis
    - Chronic sinusitis with postnasal drainage
    - Infectious causes, such as pertussis
    - Psychogenic or habit cough
- Other diagnoses to consider
  - Heart failure
  - Immunodeficiency
  - Parasitic diseases
  - Bronchiolitis caused by viral pathogens
  - Sinusitis

DIAGNOSTIC APPROACH

- For a diagnosis of asthma, the pediatrician must determine
  - Recurrent, episodic symptoms of airflow obstruction, such as cough, wheezing, shortness of breath, or chest tightness.
  - Airway flow obstruction or airflow limitation that is at least partially reversible by administration of a bronchodilator.
  - Alternative diagnoses are excluded.
- Objective measures of lung function enable the pediatrician to
  - Diagnose airflow obstruction, as well as reversibility.
  - Monitor changes over time, including daily variations.
  - Manage exacerbations, including those resulting in severe airway obstruction.

LABORATORY FINDINGS

- Evaluation for potential inhalant allergen triggers, particularly in persistent asthma.
  - Assessment of sensitivity to environmental allergens using in vivo (skin testing) or in vitro (specific immunoglobulin E [IgE]) methods
- Sputum and nasal eosinophil evaluation is not commonly performed in children.
- White cell count and differential and quantitative immunoglobulins to rule out immune dysregulation.
- Sweat chloride to rule out cystic fibrosis.
- A significant association exists between serum IgE level and the development and severity of asthma.

IMAGING

- A baseline chest radiograph may help exclude conditions that mimic asthma.
  - Routine and repetitive chest radiographs during asthma exacerbations are not recommended.

DIAGNOSTIC PROCEDURES

- Spirometry
  - Spirometric measures of airflow and lung volumes during forced expiratory maneuvers are strongly recommended as standard of care for diagnosis and monitoring.
  - Pre- and post-bronchodilator spirometry, particularly in children who are poor perceivers of airflow, are strongly recommended to confirm diagnosis, classify disease severity, and illuminate pathophysiologic processes.
  - Generally preferred to peak flow monitoring because peak flow measurements
    - Primarily assess large airway function.
    - Require establishment of individual baseline values to facilitate interpretation.
    - Are effort dependent.
  - Spirometry should be performed by trained personnel before inhalation of short-acting bronchodilator and 15–20 minutes after.
    - Helps determine presence and degree of airflow obstruction of large and small airways
    - Helps establish reversibility

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- Key measurements
  - Forced vital capacity (FVC)
  - Forced expiratory volume in the first second of expiration (FEV_1)
    - Low FEV_1, as a percentage of predicted norms, is one of the criteria used to assign severity in asthma.
    - Demonstration of improvement in FEV_1 of >12% and >200 mL from baseline and of ≥10% of predicted FEV_1 after inhaled bronchodilator use is considered evidence of reversibility consistent with asthma.
  - Forced midexpiratory flow rate ($FEF_{25\%-75\%}$)
  - Examination of the flow volume loop
- Reproducible spirometric measurements (FEV_1 values within 5% on 3 attempts) are an indicator of test validity.
- Baseline spirometry should also be performed annually during follow-up.
  - In a patient with asthma, airway obstruction results in reduced airflow with forced exhalation and smaller midexpiratory airflow rates.
  - FEV_1 should be adjusted for hyperinflation typically seen in asthma.
  - In general, an FEV_1/FVC ratio <85% predicted is indicative of the presence of airflow obstruction.
- Normal baseline spirometry in a clinical scenario suggestive of asthma can be obtained.
- Children with asthma have been reported to have much better lung function compared with adult patients.
  - Recent observations have questioned the degree of improvement that signifies reversible airway hyperresponsiveness in children with asthma, with studies suggesting poor sensitivity associated with commonly used 12% cutoff in children with asthma compared with adults.
  - Lesser reversibility may be indicative of airway hyperresponsiveness in children with asthma because there is so much variability of this test in children.

■ Peak flow meter
- Inexpensive home-use device.
- Lacks sensitivity for diagnostic use.
- Reference values vary widely and according to the brand.
- Peak flow zones are established after the child has had the opportunity to monitor daily (or twice daily) for ≥2 weeks to establish his or her personal best.

■ Peak flow monitoring at home can be useful.
- It can help demonstrate airway narrowing before patients become symptomatic.
- It can help the pediatrician
  - Monitor the effect of medication addition or withdrawal.
  - Determine the effect of triggers.
  - Determine changes in lung function.
  - Determine when to seek help.

■ Provocative testing may be used to demonstrate bronchial hyperresponsiveness when the determination of asthma is difficult despite routine evaluation.
- Exercise challenges
- Methacholine challenges
- Cold air challenges
- Mannitol challenges

■ Assessment of exhaled nitric oxide, a measure of airway inflammation in allergic asthma, is gaining support as a tool in aiding the management of asthma.

CLASSIFICATION

■ The National Asthma Education and Prevention Program Expert Panel Report 3 (EPR3) (*J Allergy Clin Immunol.* 2007;120:S94–138) emphasizes asthma control in addition to asthma severity.

■ The 2 general categories are intermittent and persistent asthma, with the latter further subdivided into mild, moderate, and severe.

■ Severity is the intrinsic intensity of the disease and is emphasized for initiating therapy.
- Asthma severity is best assessed during initial evaluation and when the child is not using a controller medication.
- When classifying severity, the presence of a single feature is sufficient to categorize the patient into the most severe applicable category.

■ Asthma is classified as well controlled, not well controlled, and very poorly controlled.

■ The predisposition to risk for exacerbations should also be kept in mind.

■ National Heart, Lung, and Blood Institute guidelines for asthma severity
- Intermittent asthma
  - >80% FEV_1 and peak expiratory flow rate (PEFR) before bronchodilator use
  - <12% and 20% change, respectively, after bronchodilator use

- Mild persistent asthma
  - >80% FEV_1 and PEFR before bronchodilator use
  - >12% and 20% change, respectively, after bronchodilator use
- Moderate persistent asthma
  - 60%–80% FEV_1 and PEFR before bronchodilator use
- Severe persistent asthma
  - <60% FEV_1 and PEFR before bronchodilator use

- Symptom class: current clinical features
  - Intermittent asthma
    - Intermittent symptoms (wheeze, cough, dyspnea) <2 times/wk
    - Brief exacerbations (from a few hours to a few days)
    - Nighttime asthma symptoms <2 times/mo
  - Mild persistent asthma
    - Intermittent symptoms (wheeze, cough, dyspnea) >2 times/wk but <1 time/d
    - Exacerbations that may affect activity and sleep
    - Nighttime asthma symptoms >2 times/mo but <1 time/wk
  - Moderate persistent asthma
    - Symptoms (wheeze, cough, dyspnea) daily
    - Exacerbations >2 times/wk; may last days and affect activity
    - Nighttime asthma symptoms >1 time/wk
  - Severe persistent asthma
    - Continuous symptoms
    - Frequent exacerbations
    - Frequent nighttime asthma symptoms
    - Physical activities limited by asthma symptoms
- Patients with intermittent asthma experiencing severe exacerbations requiring hospitalization should be treated as having moderate persistent asthma.
- Children requiring intensive care should be treated as having severe persistent asthma.
  - These children should be referred to an asthma specialist.
- Classification can change over time.
  - Ongoing review of symptoms and treatment plan every 1–6 months is helpful.

TREATMENT APPROACH

Goals of Asthma Therapy

- Reduction in impairment and risk.
- Impairment refers to
  - The intensity and frequency of asthma symptoms
  - The degree to which the patient is limited by the symptoms
- Specific goals for reducing impairment include
  - Freedom from frequent or troublesome symptoms of asthma, especially those that disturb sleep
  - Minimal need (<2 times/wk) for inhaled short-acting β-agonists (SABAs) to relieve symptoms
  - Optimization of lung function
  - Maintenance of normal daily activities, including work, school, participation in athletics, and physical activity
  - Satisfaction with asthma care on the part of the patient and family
- Reduction of risk associated with asthma and its treatment
  - Prevention of recurrent exacerbations and need for emergency department (ED) visits or hospital care
  - Prevention of reduced lung growth and loss of lung function
  - Optimization of pharmacotherapy with minimal or no adverse effects

Asthma Management

Component 1: Regular Assessment and Monitoring

- Asthma control should be checked at every visit.
- Based on a combination of multiple parameters, including FEV_1, peak expiratory flow, daily symptom scores, β_2-agonist use, nocturnal symptoms, and activity limitations.
- Objective measurements of lung function include spirometry and peak flow monitoring.
- The National Asthma Education and Prevention Program EPR3 guidelines have criteria for 3 age groups—0–4 years, 5–11 years, and ≥12 years—for the evaluation of severity and control.
- Several recommended standardized questionnaires to assess asthma control include
  - Asthma Therapy Assessment Questionnaire (ATAQ)
  - Asthma Control Questionnaire (ACQ)
  - Asthma Control Test (ACT)
  - Asthma control score

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Component 2: Patient Education and Partnership

- Patients and families should be taught basic facts about asthma, preferably using visual props.
- Physicians should ensure that teachers and school personnel understand the plan for each child with asthma.
- The pediatrician should establish patient priorities on an individual basis and enlist family and peer support to ensure plan implementation.
- Patient education should be geared to empowering patients with self-management skills.
  - Topics should include
    - Differences between normal and asthmatic airway
    - The link between airway inflammation, hyperreactivity, and bronchoconstriction
    - Identification and abatement of triggers
    - Role and mechanism of action of long-term controller and quick reliever medications
    - Instructions on daily and step-up medication regimens in the form of written asthma action plans
    - Practical instructions on being aware of the number of doses left in the inhaler, correct technique of inhaler use along with spacer, and need to take the daily medication even when asymptomatic
  - Teach, demonstrate, and have patient and caregiver show proper technique for
    - Inhaled medication use (spacer use with metered-dose inhaler [MDI])
    - Peak flow meter (optional)
  - Tailor therapy to severity and patient preference.
    - Proactively seek out and address concerns about potential adverse effects of medications.
    - Therapy should be kept as simple as possible by limiting the number of medications and doses.
    - If patients cannot adhere to a medication regimen, investigate the reasons for their nonadherence.
- Adherence to asthma medication regimens tends to be suboptimal, with reported rates of nonadherence ranging from 30%–70%. Related issues include
  - Medication characteristics such as taste, dosing schedule, difficulties with devices, side effects, and expense
  - Health beliefs, misperception of disease severity, misunderstanding of instructions, fear of side effects, dissatisfaction with health care professionals, forgetfulness, and complacency
  - Poor physician communication, failure to monitor patients regularly, and incorrect medication and dosage

Component 3: Control of Aggravating Factors

- Environmental exposures (infectious, allergic, and irritant).
- Comorbid conditions.
- In patients with uncontrolled asthma and no overt symptoms of gastroesophageal reflux, treatment with proton pump inhibitors does not help.

Component 4: Pharmacotherapy

- A stepwise approach to asthma pharmacotherapy focuses on minimizing impairment and risk with the goals of relieving obstruction and treating underlying inflammation.
- Initial therapy is chosen based on asthma severity.
- Subsequent adjustments are made based on assessment of control and responsiveness to therapy.
- The key objective of this approach is to distinguish persistent asthma requiring daily anti-inflammatory medication from intermittent asthma.
- Step 1: Intermittent asthma can be managed with SABA rescue medication.
  - For persistent asthma the medications are defined and categorized in 2 ways.
    - Relief medication for quick relief of acute symptoms and exacerbations
      - SABAs
      - Systemic corticosteroids
      - Anticholinergic agents
    - Controller medication for long-term control of the underlying pathophysiologic mechanism of asthma
      - Inhaled corticosteroids (ICS)
      - Combination ICS and long-acting β-agonists (ICS-LABAs)
      - Leukotriene receptor antagonists (LTRAs)
      - Less commonly used agents, such as theophylline, cromolyn, and other steroid-sparing medications

- Step 2: The preferred therapy for patients with mild persistent asthma is daily inhaled low-dose corticosteroids as monotherapy.
  - Alternative medications for mild persistent asthma include LTRA (montelukast) and, rarely, cromolyn and theophylline (for older children).
- Step 3: For children <4 years with moderate to severe persistent asthma, medium-dose ICS therapy is recommended. For older children, low-dose ICS-LABA is recommended.
  - Allergen immunotherapy may be considered for children >5 years requiring step 2–4 care.
- Step 4
  - Combination therapy of medium-dose ICS-LABA is recommended only for step 4 or higher levels of uncontrolled asthma.
  - Combinations of medium-dose ICS with LTRA may also be considered for step 4 or higher treatment.
- Steps 5 and 6 (severe persistent asthma)
  - ICS-LABA combinations
  - Long-term oral steroids
  - Omalizumab if patients are >12 years
- When control has been achieved and sustained for ≥3 months, stepping down to minimum required dose to maintain control is recommended.
- If control has not been attained, the therapy may be increased by 1 step if not well controlled, or by 2 steps if asthma is very poorly controlled, with close monitoring.

Approach to Difficult-to-Manage Disease

- Five issues should be assessed when dealing with a patient who does not respond to reasonable therapy.
  1. Is it asthma?
     - Anatomic lesions or other medical conditions should be ruled out.
  2. Is the patient adherent to the medication regimen?
     - Is the patient's technique for the medication delivery appropriate?
  3. Did the patient run out of medication and not realize it or say so?
  4. Is a continual exposure present, environmental or otherwise, which is continuing to cause problems for the patient?
  5. A referral or a second opinion from a specialist should be considered if the desired effect is not being achieved.

SPECIFIC TREATMENTS

Short-term Pharmacologic Therapy

- Quick relief of symptoms.
- SABAs are the most well known in this category.
  - Bronchodilation.
  - Broncho-protection.
  - Can prevent exercise-induced bronchospasm.
  - Promote smooth muscle relaxation, decrease vascular permeability, and enhance mucociliary clearance.
  - Most common side effects include
    - Tachycardia
    - Tremor
    - Headaches
    - Palpitations
    - Hypokalemia
    - Hyperglycemia
- Examples
  - Albuterol (Proventil HFA, ProAir HFA)
    - MDI: 108 mcg/puff
    - 2 puffs, 15 minutes before exercise
    - 2 puffs, 3–4 times/d, as needed
  - Albuterol (Ventolin HFA)
    - MDI: 100 mcg/puff
    - 2 puffs, 15 minutes before exercise
    - 2 puffs, 3–4 times/d, as needed
  - Albuterol (AccuNeb)
    - Nebulizer solution: 0.63 mg/3 mL; 1.25 mg/3 mL
    - 0.63–1.25 mg, 3–4 times/d, for ages 2–12 years
  - Albuterol sulfate
    - Nebulizer solution: 2.5 mg/3 mL; 0.083% (unit dose)
    - 0.05 mg/kg (min: 1.25 mg; max: 2.5 mg), 3–4 times/d
  - Levalbuterol (Xopenex)
    - Nebulizer solution: 0.31 mg/3 mL; 0.63 mg/3 mL; 1.25 mg/3 mL
    - 0.31–0.63 mg, 3 times/d, for maintenance
    - 1.25 mg, 3 times/d, for acute bronchospasm and patients who are unresponsive to lower dose
  - Levalbuterol (Xopenex HFA)
    - MDI: 45 mcg/puff
    - 1–2 puffs up to every 4 hours
  - Pirbuterol (Maxair)
    - MDI: 200 mcg/puff
    - 2 puffs 3–4 times/d, as needed

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- A short course of oral corticosteroid is a quick-relief medication.
  - Broad anti-inflammatory effects
  - Usually given for 3–10 days to
    - Gain initial control of asthma.
    - Speed resolution of moderate to severe persistent exacerbations.
  - Methylprednisolone (Medrol)
    - Tablets: 4, 6, 8, 16, 24, 32 mg
    - Short-course (3–10 days) 4 burst: 1–2 mg/kg/d (max: 60 mg/d)
  - Prednisolone
    - Tablet: 5 mg
    - Short-course (3–10 days) 4 burst: 1–2 mg/kg/d (max: 60 mg/d)
  - Prednisolone (Pediapred)
    - Liquid: 5 mg/5 mL
    - Short-course (3–10 days) 4 burst: 1–2 mg/kg/d (max: 60 mg/d)
  - Prednisolone (Prelone syrup)
    - Liquid: 15 mg/5 mL
    - Short-course (3–10 days) 4 burst: 1–2 mg/kg/d (max: 60 mg/d)
  - Prednisolone (Orapred ODT)
    - Chewable tablets: 10, 15, 30 mg
    - Short-course (3–10 days) 4 burst: 1–2 mg/kg/d (max: 60 mg/d)
  - Prednisone
    - Tablets: 1, 2.5, 5, 10, 20, 50 mg
    - Liquid: 5 mg/5 mL
    - Short-course (3–10 days) 4 burst: 1–2 mg/kg/d (max: 60 mg/d)
  - Prednisone (Prednisone Intensol)
    - Liquid: 5 mg/5 mL
    - Short-course (3–10 days) 4 burst: 1–2 mg/kg/d (max: 60 mg/d)
- Anticholinergic agents, in combination with a β-agonist, have a positive effect on acute asthma exacerbations.
  - The most common agent is ipratropium.
    - Decreases vagal tone, leading to bronchodilation
    - Blocks reflex bronchoconstriction to irritants
    - Has no effect on early- or late-phase response
    - Acts an additive to a β-agonist
  - Ipratropium bromide (Atrovent HFA)
    - MDI: 17 mcg/puff
    - Nebulizer solution: 0.20 mg/mL; 0.02% (ampule)
    - 1–2 puffs 4 times/d or 1 ampule 4 times/d
  - Ipratropium bromide/albuterol (DuoNeb)
    - Nebulizer solution: 0.20 mg/mL/2.5 mg albuterol (ampule)
    - 1 ampule 4 times/d
  - Excessive reliance on quick relievers has been associated with increased risk for death or worsening asthma.
  - Use of >1 canister per month is associated with poorly controlled asthma and risk for exacerbations.
- Use of >2 canisters of albuterol per month is associated with risk for fatal asthma exacerbations.
- Most canisters have 200 inhalations in each unit (100 doses of 2 puffs each); hence, close monitoring of SABA use may help detect patients unable to recognize inadequate asthma control.
- It is important that patients keep close track of the number of inhalations used per canister, particularly for inhalers without a built-in counter.
- Anticholinergic agents in combination with albuterol have been shown to have a positive effect on reducing the rate of hospitalizations during acute asthma exacerbations, although, singly, they are less potent than SABAs.
  - These drugs have broad anti-inflammatory effects and are usually used as a short 3- to 5-day course to gain initial control of asthma and to speed resolution of moderate or severe persistent exacerbation.
  - The available preparations—prednisone, prednisolone, and methylprednisolone—are rapidly and completely absorbed, with peak plasma concentrations occurring within 1 to 2 hours.
    - They are typically administered in a dose of 1–2 mg/kg/d.
  - The most common anticholinergic agent in use is ipratropium bromide because it is available in MDI and nebulized forms and has limited central nervous system side effects.
    - This agent decreases vagal tone (resulting in bronchodilation) and blocks reflex bronchoconstriction to irritants.
- Requirement of <2 corticosteroid courses per year is one of the criteria indicating well-controlled asthma.
- Dexamethasone
  - Recently, the use of 1–2 doses in the ED setting as equivalent therapy to prednisone/prednisolone for acute asthma exacerbations in pediatric patients was explored.

- No significant difference in relative risk for relapse
- Palatability and large quantity of the liquid dexamethasone preparation that needs to be ingested may be a limitation to its widespread use among children.

- Levalbuterol, the racemic (*R*)- isomer, has been observed by some investigators to have fewer systemic effects for the same degree of bronchodilation than albuterol, with others reporting negligible clinical effect.
- LABAs, such as salmeterol and formoterol, are not currently recommended for use as quick-relief inhalers because of US Food and Drug Administration (FDA) concerns about increasing the risk for severe asthma exacerbations.

Long-term Pharmacologic Therapy

- Treat the underlying inflammatory disorder.
- Issues to consider include
  - Drug delivery device
  - Dose level
  - Formulation of the preparation
  - Bioavailability
  - Potency of the ICS
  - Deposition in the pulmonary system or in the gastrointestinal system
- Strategies to minimize side effects include
  - Using the lowest dose needed to control asthma
  - Using less bioavailable formulations
  - Using spacers or holding chambers with MDI
  - Rinsing the mouth after inhalation
  - Adding LABA to a low to medium dose of ICS rather than increasing ICS
  - Monitoring growth
  - Ensuring age-appropriate dietary intake of calcium and exercise
- Patients may relapse when ICS are reduced or discontinued; hence, regular monitoring is recommended.

ICS

- ICS are the most effective long-term anti-inflammatory medications currently available and are recommended as the first-line treatment for most types of persistent asthma.
  - Available in
    - MDI
    - Dry powder inhaler (DPI)
    - Nebulizer
  - Improves long-term symptoms in pulmonary function
  - Reduces the need for quick-relief medications
- Major issues and concerns include
  - Growth delay
  - Ocular problems, such as cataracts and potential glaucoma
  - Thrush
  - Contraindicated during certain infections (eg, herpes simplex)
- Budesonide inhalation suspension (Pulmicort Flexhaler)
  - Approved for nebulization by the FDA
  - May be used in infants as young as 12 months.
  - DPI: 90 mcg/inhalation
    - Low dose: 2–4 inhalations/d, once daily or divided twice daily
    - Medium dose: 6–8 inhalations/d, divided twice daily
  - DPI: 180 mcg/inhalation
    - Low dose: 1–2 inhalations/d, once daily or divided twice daily
    - Medium dose: 3–4 inhalations/d, divided twice daily
    - High dose: 8 inhalations/d, divided twice daily
- Budesonide (Pulmicort Respules)
  - Liquid: 0.25 mg/2 mL; 0.5 mg/2 mL
    - Low dose: 0.5 mg, once or twice daily
    - High dose: 1.0 mg, once or twice daily
- Beclomethasone dipropionate (QVAR HFA)
  - MDI: 40 mcg/puff
    - Low dose: 1–4 puffs/d, divided twice daily
    - Medium dose: 4–8 puffs/d, divided twice daily
  - MDI: 80 mcg/puff
    - Low dose: 1–2 puffs/d, divided twice daily
    - Medium dose: 2–4 puffs/d, divided twice daily
    - High dose: 8 puffs/d, divided twice daily
- Flunisolide (AeroBid, AeroBid M)
  - MDI: 250 mcg/puff
    - Low dose: 2–4 puffs/d, divided twice daily
    - Medium dose: 4–6 puffs/d, divided twice daily
    - High dose: 8 puffs/d, divided twice daily
- Fluticasone propionate (Flovent)
  - MDI: 44 mcg/puff
    - Low dose: 2–4 puffs/d, divided twice daily
  - MDI: 110 mcg/puff
    - Medium dose: 2–4 puffs/d, divided twice daily
  - MDI: 220 mcg/puff
    - Medium dose: 2 puffs/d, divided twice daily
    - High dose: 3–8 puffs/d, divided twice daily

- DPI: 50 mcg/inhalation
  - Low: 2–4 inhalations/d, divided twice daily
- DPI: 100 mcg/inhalation
  - Medium: 2–4 inhalations/d, divided twice daily
- DPI: 250 mcg/inhalation
  - Medium: 2 inhalations/d, divided twice daily
  - High: 3–8 inhalations/d, divided twice daily

- Mometasone furoate (Asmanex Twisthaler)
  - DPI: 220 mcg/inhalation
    - Low dose: 1 inhalation/d, at night
    - Medium dose: 2–3 inhalations/d, once (at night) or divided twice daily
    - High dose: 4 inhalations/d, divided twice daily
- Triamcinolone (Azmacort)
  - MDI: 200 mcg/puff
    - Low dose: 4–8 puffs/d, divided 3–4 times/d
    - Medium dose: 8–12 puffs/d, divided 2–4 times/d
    - High dose: 12–16 puffs/d, divided twice daily

ICS-LABA

- Fluticasone propionate and salmeterol (Advair)
  - DPI
    - 100 mcg/50 mcg inhalation
      - Low dose: 1 inhalation, twice daily
    - 250 mcg/50 mcg inhalation
      - Medium dose: 1 inhalation, twice daily
    - 500 mcg/50 mcg inhalation
      - High dose: 1 inhalation, twice daily
  - MDI
    - 45 mcg/21 mcg puff
      - 2 puffs, twice daily
    - 115/21 mcg/puff
      - 2 puffs, twice daily
    - 230/21 mcg/puff
      - 2 puffs, twice daily

Nonsteroidal Anti-inflammatory Agents

- Cromolyn sodium (Intal)
  - Mast cell stabilizer
  - Decreases early- and late-phase response after allergen challenge
  - Has a good safety profile
  - Can be dispensed as a nebulizer solution or
    - Nebulizer: 20 mg/2 mL in an ampule
      - 1 ampule, 3–4 times/d
    - MDI: 1 mg/puff
      - 1–2 puffs, 3–4 times/d
      - This dose may be inadequate to affect airway hyperresponsiveness.
- Tilade
  - Has a good safety profile
  - Poor patient compliance with this medication due to its unpleasant taste
  - MDI: 1.75 mg/puff
    - 1–2 puffs, 2–4 times/d

Leukotriene Modifiers

- Block synthesis of leukotrienes or block leukotriene D4 receptors.
- Only montelukast (>6 months) and zafirlukast (>5 years) are FDA approved for children.
- As single agents, they are considered "alternate" therapy in mild persistent asthma.
- They can also be used with ICS.
- Can be administered orally.
- Improve symptoms and pulmonary function.
- Can negatively affect the pharmacokinetics of certain medications.
- Recent post-marketing reports have raised awareness about potential for neuropsychiatric and behavioral effects of montelukast.
  - Headaches
  - Agitation
  - Nightmares
  - Oppositional behavior
  - Anxiety and depression
  - Suicidal thinking and behavior
- Montelukast (Singulair)
  - Sprinkles: 4 mg for ages 12–23 months
  - Tablet
    - 4 mg, chewable, for ages 2–4 years
    - 5 mg, chewable, for ages 6–14 years
    - 10 mg, for ages >14 years
  - 1 tablet or packet in the evening for all dose formulations
- Zafirlukast (Accolate)
  - Tablet
    - 10 mg for ages 7–11 years
    - 20 mg for ages ≥12 years
  - 1 tablet, twice a day; take 1 hour before or 2 hours after meals.
- Zileuton (Zyflo Filmtab)
  - 600 mg for ages ≥12 years
  - 1 tablet, 4 times/d

LABAs

- Relaxes the bronchial smooth muscle.
- Formoterol has a quick onset of action, whereas salmeterol has a longer onset of action.

- Fixed-dose combination therapy of ICS-LABA (fluticasone/salmeterol, budesonide/formoterol, mometasone/formoterol) is available and is recommended over using separate inhalers.
- Major indication is as an add-on agent when asthma is uncontrolled by ICS therapy alone.
  - In those patients, ICS-LABA combination therapy has been shown to be synergistic and superior to increasing ICS dose, in terms of efficacy and minimizing steroid-induced side effects.
- The FDA requires all LABA-containing medications to carry a black box warning about potential for worsening asthma while on therapy.
- The FDA also specifies that LABAs should be discontinued when asthma control is achieved, and asthma control should be maintained with controllers such as ICS.
- Only available as DPIs.
- Salmeterol (Serevent Diskus)
  - DPI: 50 mcg/blister
  - 1 inhalation, twice daily
- Formoterol (Foradil Aerolizer)
  - DPI: 12 mcg/capsule
  - 1 capsule inhaled twice daily, or 15 minutes before exercise
- Sustained-release albuterol (VoSpire ER)
  - Tablets: 4 mg, 8 mg
  - Maximal dose
    - 6–12 years: 4 mg, twice daily
    - ≥12 years: 8 mg, twice daily

Theophylline

- Use has diminished in children with asthma owing to need for frequent monitoring and side effects, some of which are life threatening.
  - Headaches
  - Vomiting
  - Life-threatening side effects
    - Cardiac arrhythmias
    - Seizures
- Narrow therapeutic window and requirement for frequent monitoring.
- Theophylline metabolism and serum levels are altered by fever, viral illnesses, certain drugs (eg, cimetidine, erythromycin), and liver disease.
- Considered, rarely, for use in recalcitrant severe asthma, particularly for reduction of nocturnal symptoms.
- Suggested target peak levels are 5–10 mcg/dL as opposed to the higher levels (10–20 mcg/dL) that were previously used.
  - Serious adverse effects are much less common with this dosing strategy.
- Uniphyl, Theo-24
  - Capsules: 100, 125, 200, 300, 400, 600 mg
  - Starting dose: 10 mg/kg/d
- Elixophyllin
  - Liquid: 80 mg/15 mL
  - Maximal dose (for infants <1 year): (0.2 x age in weeks) + 5 = mg/kg/d
- Theo-Dur
  - 50, 75, 125, 200 mg sprinkles
  - Maximal dose (for children ≥1 year): 16 mg/kg/d, not to exceed the adult maximum of 800 mg/d.

Omalizumab

- Omalizumab is an anti-IgE humanized monoclonal antibody.
- FDA approved for children ≥12 years with
  - Moderate to severe asthma
  - Documented hypersensitivity to a perennial aeroallergen
  - Inadequate disease control with ICS or oral corticosteroids
- Prescribed only by asthma specialists.
  - Administered every 2 to 4 weeks subcutaneously.
  - Dose depends on the patient's weight and serum IgE level.
- Has been shown to
  - Improve lung function.
  - Significantly reduce sputum eosinophil counts.
  - Improve quality of life.
- Hypersensitivity reactions (including anaphylaxis) have been variably reported.
  - FDA has mandated a black box warning of potentially serious anaphylactic reactions with its use.
- Increased risk for cardiac and brain adverse events, particularly in adults, and a question of cardiac effects in adults.

A

WHEN TO ADMIT

- Children who are moderately to severely ill on arrival and unresponsive to β-agonist rescue therapy
- Continued symptoms despite treatment
  - Significant wheezing and retracting (eg, hunched posture, chest and neck pulling in)
  - Trouble speaking
  - Gray or blue lips or fingernails
  - Altered mental status, such as drowsiness or agitation
  - Peak flows <50% of personal best
  - Requiring β-agonists every 2–3 hours
- Continued need for supplemental oxygen despite initial therapy
- Additional factors
  - Use of β_2-agonists/glucocorticoids before ED visit
  - History of poor adherence to the medical regimen
  - Caregiver inability to provide careful medical care and supervision at home
  - Inadequate access to medical care
  - History of rapid progression of severity in past exacerbations

WHEN TO REFER

- A child >5 years requires step 4 care or higher.
- A child <5 years requires step 3 care or higher.
- A child has life-threatening asthma exacerbation or intensive care admission.
- Goals of therapy have not been met after 3–6 months of treatment.
- Diagnosis or management is complicated by comorbid conditions (eg, sinusitis, nasal polyps, severe rhinitis, uncontrolled gastroesophageal reflux, vocal cord dysfunction).
- Additional diagnostic tests are needed (eg, allergy skin testing, bronchoscopy).
- Allergen immunotherapy is a consideration.
- The asthma is difficult to control.
- Occupational triggers are suspected.
- Psychological or psychiatric issues are suspected.

FOLLOW-UP

- Effective asthma management requires a proactive, preventive approach because it is a chronic disease.
- Follow-up visits are recommended
  - Every 2–6 weeks until good asthma control is achieved
  - Then 2–4 times per year, depending on the attainment of control
- Domains assessed at each visit should include
  - Signs and symptoms
  - Pulmonary function
  - Quality of life
  - Exacerbations
  - Adherence to treatment
  - Medication side effects
  - Patient satisfaction with care
- Ongoing education should be provided to reinforce the medication regimen and technique of administration.
  - Keep therapy as simple as possible.
    - — Limit number of medications.
    - — Limit number of doses.
- Physical activity should be encouraged.
  - Use appropriate medications to prevent exercise-induced symptoms.
  - Allow students to carry and administer medication (eg, SABAs) at school with parent and physician approval.

COMPLICATIONS

- The major concern with long-term use of ICS is growth delay, with a recent study suggesting a decrease in height of up to half an inch.
- Other potential side effects of long-term ICS use include osteoporosis and, in the older population, ocular problems such as cataracts and glaucoma.
- The most common side effect is oral candidiasis.

Ataxia

DEFINITION

- Ataxia refers to disorders marked by the absence of coordinated movement, often involving gait.

HISTORY

- In pediatric patients, ataxia typically presents acutely.
- Explore evidence of
  - Recent or recurrent infection: fever, rash, respiratory symptoms, vomiting
  - Possible toxic exposures: medication, alcohol, illicit drugs
  - Trauma, observed or unobserved
- Associated symptoms can guide history.
- Change in mental status can signal a systemic process.
- Signs (early, late, or intermittent) of elevated intracranial pressure from hydrocephalus in the setting of posterior fossa mass may include
  - Headaches
  - Recurrent vomiting
  - Visual loss or diplopia
  - Worsening of symptoms when supine
- Recent and abrupt onset of symptoms suggests vascular, toxic, or infectious cause.
- Tumors and immune-mediated processes are typically subacute in progression.
  - Tumors that hemorrhage are the exception.
  - Tumor symptoms are usually reported to have developed over the course of days; however, subtle signs of weakness or lack of coordination may have been present for weeks or months.
- In acute cerebellitis (acute cerebellar ataxia), ataxia is most prominent on awakening and improves over hours to days.
- Migraine may manifest primarily as vertigo in the very young and in teenaged girls.
  - Family history of migraine, propensity to motion sickness, normal neurologic examination
  - In children <4 years: abrupt onset of unsteadiness lasting seconds to minutes
  - In adolescents: isolated vertigo or headache and vertigo
- Labyrinthitis presents as acute onset of ataxia and nystagmus.
  - Children appear more ill than in acute cerebellar ataxia.
  - Prominent vomiting and purposeful stillness to avoid provoking symptoms.
  - Frequently seen in clusters of individuals, primarily in spring and early summer, supporting an infectious (viral) cause.

PHYSICAL EXAMINATION

- A normal neurologic examination is a pertinent negative finding.
- Involvement of brain stem and cerebellar structures in acute ataxia typically results in abnormalities in history and physical examination.
- Move from the least to most invasive elements of examination, as child may be uncooperative.
- Vital signs.
- General observations: Is child uncomfortable? Agitated? Careful not to move?
- Evidence of meningismus: neck stiffness, photophobia, discomfort with movement.
- Behavioral changes: decreased alertness, inattention, dysarthria.
- Eyes: abnormal movements; examine fundi, if possible, for papilledema.
- Gait difficulties, standing posture.
  - Romberg sign to examine dorsal columns is positive when swaying or a fall occurs.
- Asymmetric or unilateral weakness.

DIFFERENTIAL DIAGNOSIS

- The initial goal in establishing a diagnosis is localizing the level of dysfunction, from brain to muscle, causing the ataxia.
- When acute stroke is suspected, emergent neurologic and neurosurgical evaluation is critical.
  - Associated symptoms include headache, seizure, or visual loss.
- Acute demyelinating encephalomyelitis
  - Prodrome: fever, vomiting, headache, malaise
  - Neurologic features: unilateral or bilateral pyramidal signs (60%–95%), acute hemiplegia (76%), ataxia (18%–65%), cranial nerve palsies (22%–45%), visual loss from optic neuritis (7%–23%), seizures (13%–35%), spinal cord involvement (24%)
- Tumors
  - Signs of obstruction of cerebrospinal fluid (CSF) are common.
  - Children <2 years usually present with increasing head circumference.
  - Older children more commonly report symptoms of headache and ataxia.
  - Weakness or sensory loss referable to lower or upper extremities, depending on spinal level, will be present with preservation of reflexes in less common spinal tumors.

- Toxic ingestion
  - Symptoms can be nonspecific.
  - When suspected, evaluate for other evidence of metabolic aberrations such as hypoglycemia, hyponatremia, and hyperammonemia.
- Sensory or motor ataxia
  - Guillain-Barré syndrome
    - When suspected, 3 disorders should be considered.
      - Transverse myelitis—distinguished from Guillain-Barré syndrome by sustained sphincter dysfunction and sensory level.
      - Tick paralysis—especially in late spring or summer; removal of a tick seen on careful inspection is usually curative.
      - Brain stem encephalitis—can mimic Fisher syndrome.
    - Typically presents as symmetric weakness.
    - In acute progressive ataxia, early clues include distal paresthesias or numbness.
    - Younger children may present with prominent symptoms of leg pain, agitation, vomiting, meningeal signs, and reflexes that are depressed or absent.
- Recurrent episodes of acute cerebellar ataxia suggest (most common)[1]
  - Migraine or migraine equivalents
    - Basilar migraine (most common)
    - Benign paroxysmal vertigo
    - Benign paroxysmal torticollis of infancy
    - Alternating hemiplegia of childhood
  - Metabolic disorders
    - Mitochondrial disorders
      - Pyruvate decarboxylase deficiency
      - Pyruvate dehydrogenase deficiency
      - Leigh disease (subacute necrotizing encephalomyelopathy)
    - Aminoacidopathies
      - Maple syrup urine disease, intermittent form Hartnup disease
      - γ-Glutamylcysteine synthetase deficiency
    - Urea cycle disorders
      - Carbamoyl phosphate synthetase type 1 deficiency
      - Ornithine transcarbamylase deficiency
      - Citrullinemia
      - Argininosuccinic aciduria
    - Organic acidopathies
      - Holocarboxylase deficiency
      - Biotinidase deficiency
      - Isovaleric acidemia
    - Carnitine acetyltransferase deficiency
  - Recurrent genetic ataxias
    - Episodic ataxia type 1 (paroxysmal ataxia with myokymia)
    - Episodic ataxia type 2 (acetazolamide responsive)
    - Episodic ataxia types 3 and 4
    - Episodic ataxia with paroxysmal dystonia
    - CAPOS syndrome (**c**erebellar ataxia, **a**reflexia, **p**es cavus, **o**ptic atrophy, **s**ensorineural hearing loss)
  - Nonconvulsive seizures
  - Drug ingestion (most common)
  - Paroxysmal tonic upgaze of childhood
  - Cogan syndrome

LABORATORY EVALUATION

- Thorough history and physical examination often make laboratory testing unnecessary.
- Consider urine toxicology at a minimum; where there is high suspicion, hold blood and urine samples for targeted analysis following consultation with poison control.

IMAGING

- Brain imaging is indicated in the presence of focal neurologic examination or inability to perform reliable examination because of illness or sedation.
- Neurologic consultation should be obtained before ordering imaging.
- Head computed tomography (CT) effective in
  - Hemorrhage
  - Hydrocephalus
  - Patients with a known brain tumor and acute change in mental status or acute ataxia
- Magnetic resonance imaging is a more sensitive demonstration of brain parenchyma without radiation exposure to the child.
  - Contrast studies are indicated for possible infection, inflammation, or tumor.
  - Magnetic resonance angiography or venography to image vasculature in possible stroke.

DIAGNOSTIC PROCEDURES

- Lumbar puncture should be considered in suspected infectious or inflammatory processes.
  - Acute cerebellar ataxia
    - Normal white blood cell count or mild pleocytosis is typical.
  - Bacterial meningitis or encephalitis should be considered with
    - Significant pleocytosis or low glucose

- Guillain-Barré syndrome
  - — Demonstrates dissociation between cells and protein with elevated protein and borderline to normal white blood cell counts.
  - — CSF may be normal on initial presentation.

TREATMENT APPROACH

- Treatment is directed at the underlying diagnosis.

SPECIFIC TREATMENT

- Acute stroke
  - Decompression of posterior fossa hemorrhage
- Acute disseminated encephalomyelitis
  - Consider immune-modulating therapy such as steroids, intravenous immunoglobulin, or plasma exchange.
  - Immunologic therapy may hasten recovery but does not seem to affect ultimate outcome.
- Infections such as cerebellar abscess or brain stem encephalitis
  - Initial treatment with broad antimicrobial therapy as well as antiviral therapy (acyclovir for herpes simplex infection) until causative agent is identified
- Guillain-Barré syndrome
  - Treatment with intravenous immunoglobulin (preferred) or plasma exchange.
  - Intravenous immunoglobulin should not be used in patients who are IgA deficient.
- Acute cerebellar ataxia
  - Full recovery is typical but can take as long as 3–6 months.
  - No evidence that immune therapy, such as steroids, alters outcome.

WHEN TO REFER

- Neurologic consultation
  - Posterior fossa hemorrhage—urgent consultation
  - Ischemic stroke
  - Brain tumors—also neurosurgery and oncology

WHEN TO ADMIT

- Ischemic stroke
  - Admission to pediatric critical care
- Guillain-Barré syndrome
  - For monitoring of vital signs and respiratory function

FOLLOW-UP

- Follow-up 2–4 weeks after discharge to monitor recovery.
- Persistent or permanent dysfunction may warrant physical therapy and adaptive devices.

PROGNOSIS

- Prognosis is usually good and is dependent on specific diagnosis.
- In cases requiring admission, early recognition leading to early admission and treatment may improve outcomes.

PREVENTION

- Aside from ingestions, few of the causes of ataxia are preventable.

REFERENCE

1. From Ryan MM, Engle EC. Topical review: acute ataxia in childhood. *J Child Neurol.* 2003;18(5):309–316, with permission from SAGE Publications

Atopic Dermatitis

DEFINITION

- Atopic dermatitis (AD) is a multifactorial dermatologic condition involving chronic inflammation of the skin.
- Sometimes referred to as *eczema,* a general term to describe skin that is erythematous, scaling, vesicular, and crusting.
- May be the initial condition signaling the progression to further allergic disease, known as the *atopic march.*
- Associated immunoglobulin E (IgE)-mediated diseases
  - Allergic rhinitis
  - Asthma
  - Food allergies

SIGNS AND SYMPTOMS

Acute Dermatitis

- Associated with
  - Severe pruritus
  - Redness
  - Vesicles
  - Exudation
  - May have subacute pattern of pruritus, redness, and scaling

Chronic Lesions

- Marked by
  - Excoriations
  - Lichenification (thickened skin and deeper or exaggerated skin lines)
  - Postinflammatory hypopigmentation or hyperpigmentation

Infantile AD

- Eruption of erythematous papules on facial cheeks and extensor surfaces of arms and legs
- Dry hair, scaly scalp (often)

Childhood AD

- Begins at ~3 years and lasts through puberty
- The areas most affected include
  - Antecubital and popliteal folds
  - Neck
  - Flexor surfaces of wrists and ankles
  - More subacute and chronic dermatitis

Adult AD

- Additional clinical signs include
  - Diffuse involvement of the body
  - Xerosis
  - Lichenification
  - Central facial pallor

Other Clinical Manifestations

- Keratosis pilaris
  - Characteristic goose flesh appearance secondary to multiple, small, skin-colored or mildly erythematous keratotic papules located on upper arms, thighs, and facial cheeks
- Lichen spinulosus
  - Tiny hairlike spines top the small papules that occur in crops on various locations.
- Pityriasis alba
- Morgan folds
- Urticaria
- Hyper-linear palms
- Juvenile plantar dermatosis
  - Mainly affects the feet, rarely the hands
  - Produces shiny, fissured skin on the plantar surfaces
- Nummular eczema
- Cataracts (anterior subcapsular, to distinguish from those of secondary corticosteroids)

DIFFERENTIAL DIAGNOSIS

- Seborrheic dermatitis.
- Seborrhea is associated with scaling, commonly on the scalp and forehead and around the eyebrows.
- Can be accompanied by pruritus.
- Contact dermatitis (allergic and irritant forms).
  - Diagnosis often requires positive exposure history to the potential offending agent.
  - Limited in distribution on the body to the area of contact.
  - More likely to have acute onset and localized appearance.
- Psoriasis.
- Scabies.
- Dermatophyte infection.
- Systemic immunologic or metabolic disorders.
  - Wiskott-Aldrich syndrome
  - Leiner disease
  - Histiocytosis X
  - Ataxia
  - Telangiectasia
  - Histidinemia
  - Agammaglobulinemia
  - Hartnup disease
  - Hurler syndrome
  - Eosinophilic gastroenteritis
  - Acrodermatitis enteropathica
  - Phenylketonuria

DIAGNOSTIC APPROACH

- Diagnosis is determined solely by history and clinical examination.
- Criteria for diagnosis (patient characteristics to look for)
  - Major criteria (all must be present)
    - Pruritus
    - Typical morphology and distribution
      - Facial and extensor involvement during infancy and early childhood
      - Flexural lichenification and linearity by adolescence
    - Chronic or recurring dermatitis
  - Minor criteria (≥2 must be present)
    - Personal or family history of atopy (eg, asthma, allergic rhinoconjunctivitis, AD)
    - Immediate skin test reactivity
    - White dermatographism or delayed blanch to cholinergic agents
    - Anterior subcapsular cataracts
  - Associated conditions (≥4 must be present)
    - Xerosis, ichthyosis, hyper-linear palms
    - Pityriasis alba
    - Keratosis pilaris
    - Facial pallor, infraorbital darkening (allergic shiner)
    - Morgan fold
    - Elevated serum IgE level
    - Keratoconus
    - Nonspecific hand dermatitis
    - Recurring cutaneous infections
- Patients may have AD and not meet these criteria.

LABORATORY FINDINGS

- No routine laboratory studies are needed for diagnosis.
- Specific tests to rule out other disorders on a case-by-case basis.
  - If infections are recurrent, consider an immunodeficiency evaluation.
- Bacterial cultures of encrusted or exudative skin lesions/nares to detect staphylococcal organisms are warranted when
  - Secondary infection is suspected.
  - Improvement is not noted with standard therapy.
- Patch testing may be considered to pinpoint potential antigenic triggers, which may add a component of contact dermatitis.
- Skin biopsy may be necessary when the definitive diagnosis is in question.

TREATMENT APPROACH

- Treatment of uncomplicated cases
  - Treatment to relieve dryness, inflammation, and pruritus and eradicate secondary bacterial infections.
  - Daily applications of emollients (cream or ointment), especially after brief warm baths.
    - Ointments are better than emollients in more severe cases.
    - If discomfort (stinging sensation) occurs or if ointment feels too occlusive (eg, in humid weather), creams can be substituted.
  - Bathing should last no longer than 5 minutes.
    - Mild soaps or non-detergent cleansers are recommended.
    - Pat dry with a towel and apply emollient immediately to all skin.
    - Apply prescription topical medicines to affected areas.
  - Inflammation is best treated with topical corticosteroids.
    - Generally, ointments tend to work better than creams.
      - Ointments remain the choice for chronic dermatitis in which dryness and lichenification predominate.
    - Creams
      - Sometimes preferred for cosmetic appeal
      - Can be used for acute weeping, erythematous lesions
- Treatment of complicated cases
  - If flares continue despite compliance with medication and appropriate skin care, a secondary infection may be responsible that requires treatment.
  - Many patients have significant colonization with *Staphylococcus aureus.*
    - If *S aureus* superinfection occurs, hospitalization for aggressive care and intravenous (IV) antibiotics may be required.
    - Skin cultures may help identify appropriate antibiotic sensitivities.
    - Application of nasal mupirocin may be necessary to eradicate bacterial carriage.
  - May also require treatment for herpes simplex infection, human papillomavirus (HPV), and molluscum contagiosum.
  - Recently, attention has been placed on barrier-repair creams providing a steroid-sparing option.

A

SPECIFIC TREATMENTS

Steroids

- Low-potency topical agents, such as 1% hydrocortisone or desonide
  - Can be used for mild disease, even on the diaper area and face.
  - Twice-daily dosing should be limited to a 2-week course or less.
- Mid- to high-potency steroids, such as triamcinolone or fluocinonide
  - Can be used in more severe cases on the trunk and extremities
- Strong, halogenated steroids
  - Should not be applied to the face, axillae, or groin.
  - Oral systemic steroid taper should rarely be prescribed.
- Most worrisome side effects
  - Dermal and epidermal atrophy.
  - Suppression of the hypothalamic-pituitary-adrenal axis.
  - Applying topical steroids to the occluded groin area of a diapered child increases the risk of systemic side effects.

Nonsteroidal Immunomodulators and Other Topical Medications

- Topical tacrolimus and pimecrolimus
  - Approved for children ≥2 years
  - Most efficacious in mild to moderate disease
  - Alternatives to topical steroids
  - Can be applied to the face
  - Theoretical risk of cancer
- Other topical medications, coal tar and doxepin, are not routinely prescribed by pediatricians.

Pharmacologic Therapy

- Antihistamines may help relieve pruritus, especially if dermatitis accompanies allergic rhinitis, urticaria, and sleep disturbance.
  - Nonsedating antihistamines, such as loratadine, can be used daily.
  - The sedating antihistamines, hydroxyzine and diphenhydramine, are most useful at bedtime.
- Efficacy of alternative medicine, such as herbal or probiotic supplementation, remains unknown.

Behavior Modification

- Teach the child to rub rather than scratch.
- Have the child wear mittens or socks on his or her hands when in bed at night to reduce the itch-scratch cycle.
- Trim the fingernails frequently to avoid trauma and infection.

Diet

- Dietary management is controversial, and changes should be made judiciously.
- Peanuts, milk, and eggs are the most common food culprits.
- If food allergies are highly likely, as determined by a pediatric allergist, strict avoidance of foods that serve as antigenic triggers should be encouraged; the most common are
  - Cow milk
  - Hen eggs
  - Soy
  - Peanuts
  - Tree nuts (and seeds)
  - Wheat
  - Fish and shellfish

Secondary Infections

- Topical or oral antibiotics.
  - Cephalexin
  - Dicloxacillin
  - Amoxicillin-clavulanate
  - Azithromycin
  - Clindamycin
  - Mupirocin (topical)
- HPV treatments.
- Vesicants.
- Immunomodulators.
- Cryotherapy.
- Ablation with carbon dioxide laser.
- Molluscum contagiosum treatments.
  - Manual expression
  - Cryotherapy
  - Topical application of cantharidin or imiquimod
- Widespread herpes infection requires treatment with IV acyclovir.

Aggressive Interventions for Severe Cases

- Prescribed at the discretion of the skin experts
  - Systemic immunomodulators
  - Ultraviolet light therapy

WHEN TO ADMIT

- Severe cases requiring systemic immunomodulation
- Extensive secondary bacterial infection requiring IV antibiotics
- Widespread herpes infection (eg, eczema herpeticum, Kaposi varicelliform eruption)

WHEN TO REFER

- Recalcitrant cases should be referred to a dermatologist or an allergist.
- Secondary HPV or molluscum contagiosum infections should be referred to a dermatologist for aggressive treatment.

COMPLICATIONS

- *S aureus* superinfection
  - Hospitalization for aggressive care and IV antibiotics may be required.
  - Skin cultures may help identify antibiotic sensitivities.
  - Application of nasal mupirocin may be necessary to eradicate bacterial carriage.
- Herpes infection, known as *eczema herpeticum* or *Kaposi varicelliform eruption*
  - Requires treatment with IV acyclovir
- HPV infection
- Molluscum contagiosum infection

PREVENTION

- AD cannot be cured, but meticulous adherence to proper skin care can control symptoms and secondary infection.
- Moisturizing of the skin with daily applications of emollients, especially after bathing, is crucial to keep the skin hydrated.
- Prophylactic avoidance of food allergens, for lactating mothers and newborns and infants via exclusive breastfeeding in the first 6 months of life, may be helpful in families with a strong family history of atopy.
- Prevention or delay of onset may be possible with use of hydrolyzed formula during first 4 to 6 months in newborns and infants who are not exclusively breastfed.

Attention-Deficit/Hyperactivity Disorder

DEFINITION

- Attention-deficit/hyperactivity disorder (ADHD) is a common neurodevelopmental disorder in children and adolescents.
- Frequently diagnosed in children with academic underachievement or behavioral problems.
- Hallmarks are hyperactivity, impulsivity, and inattention that are beyond normal developmental expectations for a child's age.
- Core symptoms interfere with attainment of many normal developmental milestones (academic, fine motor, and social and adaptive skills).

SIGNS AND SYMPTOMS

Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (*DSM-5*) Criteria for Diagnosis (Box 1)

- Combined presentation: If both Criterion A1 (inattention) and Criterion A2 (hyperactivity-impulsivity) are met for the past 6 months.
- Predominantly inattentive presentation: If Criterion A1 (inattention) is met but Criterion A2 (hyperactivity-impulsivity) is not met for the past 6 months.
- Predominantly hyperactive-impulsive presentation: If Criterion A2 (hyperactivity-impulsivity) is met and Criterion A1 (inattention) is not met for the past 6 months.
- Because symptoms can change over time, the presentation may change over time as well.
- The *DSM-5* criteria do not account for differences in presentation by age, sex, or race/ethnicity; clinicians must exercise judgment in their use of the criteria.
- Any symptoms suggestive of possible harm to self or others warrant immediate evaluation by a skilled clinician.

DIFFERENTIAL DIAGNOSIS

- Conditions that may mimic or co-occur with ADHD include
  - Developmental differences or normal variants
    - Normal variation
    - Giftedness
    - Sociocultural differences in expectations or parenting, or both
  - Medical disorders
    - Medication side effects
    - Substances of abuse
    - Hearing impairment
    - Visual impairment
    - Sleep disorders, including obstructive sleep apnea and poor sleep hygiene
    - Toxins (eg, chronic lead exposure or acute lead intoxication; chronic iron deficiency anemia)
    - Thyroid disorders
    - Chronic disease complications
  - Neurologic or developmental disorders
    - Learning disabilities
    - Autism spectrum disorder (ASD)
    - Pervasive developmental disorders
    - Tic disorders (eg, Tourette syndrome)
    - Communication disorders
    - Processing disorders
    - Intellectual disabilities (mental retardation)
    - Neurodevelopmental syndromes (eg, fetal alcohol syndrome, fragile X syndrome)
    - Cerebral palsy
    - Seizure disorders (petit mal or developmental delays)
    - Sequelae of central nervous system trauma or infection
    - Neurodegenerative disorders
    - Motor coordination disorders
  - Psychosocial or environmental problems
    - Stress in family situation (marriage, separation or divorce, birth of sibling, death)
    - Stress in environment (new home, new school)
    - Family dysfunction
    - Parenting dysfunction
    - Neglect, abuse, or both
    - Parental psychopathology
    - Parental substance use disorder
    - Inappropriate educational program
  - Emotional or behavioral disorders
    - Oppositional defiant disorder
    - Conduct disorder
    - Depressive disorders
    - Anxiety disorders
    - Bipolar disorder
    - Obsessive-compulsive disorder
    - Posttraumatic stress disorder
    - Adjustment reaction
    - Schizophrenia
- Establishing whether any medical conditions are present is paramount for primary care physicians.
  - Poor visual acuity or hearing loss
    - Can contribute to academic difficulties
  - Obstructive sleep apnea
    - May be caused by enlarged tonsils or adenoid, or both

Box 1. *DSM-5* Criteria for ADHD

A. A persistent pattern of inattention and/or hyperactivity-impulsivity that interferes with functioning or development, as characterized by (1) and/or (2):
   1. Inattention: Six (or more) of the following symptoms have persisted for at least 6 months to a degree that is inconsistent with developmental level and that negatively impacts directly on social and academic/occupational activities:
      Note: The symptoms are not solely a manifestation of oppositional behavior, defiance, hostility, or failure to understand tasks or instructions. For older adolescents and adults (age 17 and older), at least 5 symptoms are required.
      a. Often fails to give close attention to details or makes careless mistakes in schoolwork, at work, or during other activities (eg, overlooks or misses details, work is inaccurate).
      b. Often has difficulty sustaining attention in tasks or play activities (eg, has difficulty remaining focused during lectures, conversations, or lengthy reading).
      c. Often does not seem to listen when spoken to directly (eg, mind seems elsewhere, even in the absence of obvious distraction).
      d. Often does not follow through on instructions and fails to finish schoolwork, chores, or duties in the workplace (eg, starts tasks but quickly loses focus and is easily sidetracked).
      e. Often has difficulty organizing tasks and activities (eg, difficulty managing sequential tasks; difficulty keeping materials and belongings in order; messy, disorganized work; has poor time management; fails to meet deadlines).
      f. Often avoids, dislikes, or is reluctant to engage in tasks that require sustained mental effort (eg, schoolwork or homework; for older adolescents and adults, preparing reports, completing forms, reviewing lengthy papers).
      g. Often loses things necessary for tasks or activities (eg, school materials, pencils, books, tools, wallets, keys, paperwork, eyeglasses, mobile telephones).
      h. Is often easily distracted by extraneous stimuli (for older adolescents and adults, may include unrelated thoughts).
      i. Is often forgetful in daily activities (eg, doing chores, running errands; for older adolescents and adults, returning calls, paying bills, keeping appointments).
   2. Hyperactivity and Impulsivity: Six (or more) of the following symptoms have persisted for at least 6 months to a degree that is inconsistent with developmental level and that negatively impacts directly on social and academic/occupational activities:
      NOTE: The symptoms are not solely a manifestation of oppositional behavior, defiance, hostility, or failure to understand tasks or instructions. For older adolescents and adults (age 17 and older), at least 5 symptoms are required.
      a. Often fidgets with or taps hands or feet or squirms in seat.
      b. Often leaves seat in situations when remaining seated is expected (eg, leaves his or her place in the classroom, in the office or other workplace, or in other situations that require remaining in place).
      c. Often runs about or climbs in situations where it is inappropriate. (Note: In adolescents or adults, may be limited to feeling restless.)
      d. Often is unable to play or engage in leisure activities quietly.
      e. Is often "on the go," acting as if "driven by a motor" (eg, is unable to be or uncomfortable being still for extended time, as in restaurants, meetings; may be experienced by others as being restless or difficult to keep up with).
      f. Often talks excessively.
      g. Often blurts out an answer before a question has been completed (eg, completes other people's sentences; cannot wait for turn in conversation).
      h. Often has difficulty waiting his or her turn (eg, while waiting in line).
      i. Often interrupts or intrudes on others (eg, butts into coversations, games, or activities; may start using other people's things without asking or receiving permission; for adolescents and adults, may intrude into or take over what others are doing).
B. Several inattentive or hyperactive-impulsive symptoms were present prior to age 12 years.
C. Several inattentive or hyperactive-impulsive symptoms are present in 2 or more settings, (eg, at home, school or work; with friends or relatives; in other activities).
D. There is clear evidence that the symptoms interfere with, or reduce the quality of, social, academic, or occupational functioning.

A

Box 1 (*continued*)

E. The symptoms do not occur exclusively during the course of schizophrenia or another psychotic disorder, and are not better explained by another mental disorder (eg, mood disorder, anxiety disorder, dissociative disorder, personality disorder, substance intoxication or withdrawal).

Specify whether:

Combined presentation: If both Criterion A1 (inattention) and Criterion A2 (hyperactivity-impulsivity) are met for the past 6 months.

Predominantly inattentive presentation: If Criterion A1 (inattention) is met but Criterion A2 (hyperactivity-impulsivity) is not met for the past 6 months.

Predominantly hyperactive-impulsive presentation: If Criterion A2 (hyperactivity-impulsivity) is met and Criterion A1 (inattention) is not met for the past 6 months.

Because symptoms can change over time, the presentation may change over time as well.

From American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders.* 5th ed. Arlington, VA: American Psychiatric Association Publishing; 2013, with permission.

  - Can be associated with daytime somnolence, hyperactivity, and academic problems
- Medication side effects
  - May explain unusual drowsiness and lack of attention in the classroom
- Dermatologic findings (eg, café au lait spots)
  - May suggest neurofibromatosis or other neurologic disorders associated with learning and behavioral difficulties
- A history of 20–50 episodes a day of repeated staring pauses lasting several seconds
  - May occur in home and school settings
  - May indicate absence seizures

DIAGNOSTIC APPROACH

- No biological marker or gold standard diagnostic test exists that can reliably identify persons with and without ADHD.
- Ascertain whether any other disorders or factors exist that may better explain a child's symptoms and impairment.
  - Such conditions may
    - Be the primary cause of the child's behavioral and attention difficulties.
    - Increase the child's level of impairment if comorbid with ADHD.
  - Evaluation can be streamlined through a complete history and thorough physical examination.
- The American Academy of Pediatrics (AAP) recommends that children aged 4–18 years should undergo evaluation for ADHD if they exhibit any of the following signs or symptoms:
  - Inattention
  - Hyperactivity
  - Impulsivity
  - Academic underachievement
  - Behavior problems
- Diagnosing ADHD is complicated by the fact that presentations of ADHD can vary substantially.
  - In addition, many conditions, including ASD, can coexist with ADHD, further adding to variation in presentation.
- Essential step: comprehensive history, with particular attention to
  - Presenting complaint
  - Development
  - School history
  - Family history
  - Social history
- Physical examination (usually normal)
  - Can help identify other problems that may contribute to or represent the cause of behavior problems
  - May allow the opportunity to assess a child's mental status and interaction with caregivers
- Several excellent ADHD rating scales for parent and teacher respondents are commercially available to clinicians.
  - NICHQ Vanderbilt Assessment Scales
  - ADHD Rating Scale
  - Conners 3
  - SNAP-IV Rating Scale
- Co-occurring behavioral or developmental conditions often are present; all youth undergoing an evaluation for ADHD should be assessed for these conditions.
  - Take a complete history.

- Several ADHD ratings scales (ie, NICHQ Vanderbilt, Conners 3, and SNAP-IV) include items that query for symptoms of depression or anxiety, oppositional defiant, and conduct disorders.
- Rating scales exist that specifically target the assessment of particular conditions, including depression, anxiety, and disruptive behaviors.
  - Center for Epidemiological Studies Depression Scale for Children
  - Multidimensional Anxiety Scale for Children
  - Eyberg Child Behavior Inventory
- Questionnaires that review *DSM-5* criteria for most common childhood mental health disorders in one instrument.
  - Child Symptom Inventory
  - DISC Predictive Scales

■ To assess ADHD
- Step 1: Patients with behavior problems or academic difficulties undergo a complete physical examination, including hearing and vision assessments, and are given assessment materials.
  - Assessment materials may contain
    - Pediatric intake history form
    - Request for school records
    - Behavior rating scales
    - Educational materials
- Step 2: Once the results and assessment materials have been reviewed, patients may be scheduled for an evaluation.
  - Number of visits needed to complete an evaluation depends on the complexity of symptoms and amount of time available at each visit.
  - The time reported to complete the overall evaluation, review background records, provide patient and family education, and establish a treatment plan may be 90–240 minutes.
  - Offices have found multiple solutions for obtaining assessment materials and completing an evaluation, including
    - Use of written assessment or computerized packets
    - Longer appointments scheduled at designated times (eg, evenings, Saturday mornings, one particular clinic session every other week)
    - Partnerships with local schools
    - Use of affiliated health care personnel, including social workers or mental health professionals
  - AAP ADHD toolkit includes
    - NICHQ Vanderbilt Rating Scales (parent and teacher initial assessment and follow-up forms)
    - Sample cover letter to assist physicians in creating an office-based system to efficiently evaluate a child for ADHD

■ Clinicians should obtain data from schools on child's level of functioning and academic achievement.
- Results of multidisciplinary evaluations
- Individualized education programs (IEPs)
- Achievement test results
- Grades
- Written or verbal teacher narratives
- Many ADHD rating scales use teacher versions that can be used to facilitate endorsement of diagnostic criteria or to assess for other conditions by school or after-school personnel.
- If the child is homeschooled or heavily involved in after-school activities, clinicians may want to obtain information from adults overseeing these programs (eg, coaches, religious educators, after-school caregivers, tutors).

LABORATORY FINDINGS

■ Blood lead levels and thyroid hormone levels are infrequently abnormal in youth with ADHD.
- There is little evidence that these tests adequately discriminate between youth with and without ADHD.

IMAGING

■ Youth with ADHD often have abnormalities on brain imaging or electroencephalography.
- Abnormalities are not consistent.
- Do not usually represent clinically significant findings.
- Do not adequately discriminate youth with and without ADHD.

CLASSIFICATION

■ Core symptoms result in 3 distinct subtypes of ADHD recognized in *DSM-5*.
- Predominantly inattentive subtype (ADHD-IA)
  - Children with ADHD-IA often present with school underachievement and may go unrecognized by parents and teachers.

- Hyperactive/impulsive subtype (ADHD-HI)
- Subtype that includes a combination of inattentive and hyperactive/impulsive features (ADHD-CT)
  - Children with ADHD-HI or ADHD-CT commonly present with school underachievement, disruptive classroom behavior, and poor relationships with peers and family members.

TREATMENT APPROACH

- ADHD is a chronic condition that requires ongoing, collaborative care.
  - ADHD affects youth across multiple domains of functioning, and understanding the implications across these domains is important.
  - Parents are important partners in treatment because they ultimately implement any program.
  - A spectrum of health and school professionals is often involved; the child eventually has to take all of this over.
  - Strategies include educational and support groups, such as
    - Children and Adults with Attention-Deficit/Hyperactivity Disorder (CHADD)
    - Learning Disabilities Association of America
- The AAP recommends that clinicians, parents, and the child, with school personnel, identify specific target outcomes that they hope to affect with treatment.
- 3 broad treatment modalities have been recommended, most often combined (multimodal treatment).
  - Medications
  - Psychosocial interventions directed at the child in the home and school
  - Classroom assistance
  - Solid evidence exists for the use of stimulant medication, behavioral modification strategies, and their combination.
- If psychostimulants are used, medication choice, dose, and time interval must be carefully titrated to meet the individual child's needs.
  - Changes in ADHD symptoms, target outcomes, and the development of any side effects must be documented.
  - Prior to starting stimulant medications, the child should have
    - An in-depth cardiac history and physical examination
    - Follow-up electrocardiogram if indicated
    - Cardiology referral in cases with family or personal history of cardiac disease or symptoms
  - Psychiatric complications include
    - New onset or acute exacerbation of aggressive symptoms
    - Rare hallucinogenic symptoms, particularly visual hallucinations related to insects
  - Several trials may be necessary before the most effective medication (type and dose) with the fewest side effects is identified.
  - Psychostimulants should be considered second-line therapy for preschool children aged 4–5 years.
- Behavioral management interventions that seek to improve parenting practices, school function, and peer relationships decrease ADHD symptoms and impairment.
  - Parent training programs
  - Youth-focused intensive summer camp programs
  - Behavioral consultation in the classroom
- School-based services are a critical part of a comprehensive management plan.
  - Communication with school personnel is essential for diagnosis and optimal titration of medication.
  - Evidence exists for effectiveness of highly structured behavioral management strategies implemented by school staff, such as
    - Daily report cards
    - Point or token systems with primary outcomes of
      - Following classroom rules
      - Complying with teacher requests
      - Improving peer interactions
      - Increasing classwork productivity
  - Comorbid learning disabilities can be identified by school staff.
    - Specific learning interventions require an IEP, as stipulated under the Individuals With Disabilities Education Act (IDEA).
    - Learning disabilities coexistent with ADHD usually fall into the category of language-based disorders of learning or impaired mathematics performance.
- It is important to educate school personnel about ADHD-associated behaviors.
  - Motor challenges, including dysgraphia, with resultant poor handwriting
  - Problems related to poor visual-motor abilities (eg, copying materials off of a board or textbook onto paper)

- Inconsistent performance
- Delayed acquisition of core reading and math skills
- Low productivity
- Delay in rapid retrieval of facts
- Difficulty with higher-level problem-solving involving multiple steps
- Impaired reading comprehension
- Poor metacognitive abilities (eg, organization, time management, breaking tasks down into smaller components)

■ Most alternative treatment approaches lack real evidence for or against their use.
- Dietary recommendations
- Ocular training
- Hypnotic and biofeedback regimens

SPECIFIC TREATMENTS

Medications

■ Psychostimulants (methylphenidate, dextroamphetamine, and mixed salts of amphetamine) with careful medication management
- Address core symptoms and improve sustained attention, organization, and motor inhibitor control.
- Decrease disruptive behaviors (eg, fidgeting, impulsive interrupting, aggression, relational interactions, opposition).
- Increase the accuracy of performance and improve short-term memory, reaction time, and seat work computation; however, the effect is smaller than that seen for behavioral challenges.
- Are effective for ~70% of children; increases to >90% if an alternative stimulant is tried after initial failure.
- Children starting on medication should have a complete medical history (including family history of heart disease or arrhythmias, as well as symptoms of shortness of breath, chest pain, dizziness, or palpitations on exertion) and a physical examination.
- See **Table 1** for specific dosing information.

■ Psychostimulants should be considered second-line therapy for preschool children aged 4–5 years.
- A strong response to behavioral interventions without medication has been seen.
- Preschool ADHD Treatment Study guidelines support the use of stimulants if children still have moderate to severe impairment after implementing behavioral therapies.
- Dextroamphetamine has a US Food and Drug Administration indication for preschool-aged children with ADHD; there is more evidence for efficacy and safety in this age group than with methylphenidate.
- Preschool-aged children metabolize stimulants at a slower rate than older children and report more side effects.
  - — Lower doses should be prescribed to start.
  - — Dosage should be increased in smaller increments.

■ AAP guidelines recommend certain non-stimulant medications (**Table 2**) as second-line treatment of ADHD after psychostimulants for all age groups.

Risks

■ Common side effects
- Headaches
- Stomachaches
- Insomnia
- Anorexia
- Possible growth delay (~1 cm in height lost per year)
- Irritability
- Emotional lability or constriction
- Compulsive picking of the nose or skin
- Possible high abuse potential

■ Other safety concerns
- Cardiovascular
  - — Elevations in heart rate and blood pressure.
  - — Rare events, such as stroke, myocardial infarction, and sudden death, particularly in youth with preexisting cardiac disease.
  - — Youth should be monitored for the emergence of hypertension.
- Psychiatric concerns
  - — New onset or acute exacerbation of aggressive symptoms
  - — Rare hallucinogenic symptoms, particularly visual hallucinations related to bugs

Other Medications

■ Other medications may be used as second-line treatment of ADHD (see **Table 2**).

■ Selective norepinephrine reuptake inhibitor (atomoxetine)
- Common side effects include
  - — Stomachache
  - — Nausea
  - — Appetite suppression
  - — Weight loss

(continued on page 91)

Table 1. Stimulant Medications, Dosing, and Duration of Effects

Active Ingredient	Drug Name	Dosing	Duration of Behavioral Effects
Mixed salts of amphetamine (dextroamphetamine/ levamfetamine)	Adderall Tablets (scored): 5, 7.5, 10, 12.5, 15, 20, 30 mg	Start with 5 mg 1–2 times/d and increase by 5 mg each week until good control is achieved. Maximum recommended dose: 40 mg	4–6 h
	Adderall XR Extended-release capsule (can be sprinkled): 5, 10, 15, 20, 25, 30 mg	Start at 5 mg in morning and increase by 5 mg each week until good control is achieved. Maximum recommended dose: 30 mg	10–12 h
Lisdexamfetamine	Vyvanse Extended-release capsule (can be sprinkled): 20, 30, 40, 50, 60, 70 mg	Start at 30 mg in morning and increase by 10–20 mg until good control is achieved. Maximum recommended dose: 70 mg	10–14 h
Dextroamphetamine	Dexedrine Tablet: 5 mg Dextrostat Tablet (scored): 5, 10 mg	Tablet: Start with 5 mg 1–2 times/d and increase by 5 mg each week until good control is achieved. Maximum recommended dose: 40 mg	4–6 h
	Dexedrine Spansules Sustained-release capsule (cannot be chewed): 5, 10, 15 mg	Capsule: start with 5 mg 1 time/d and increase by 5 mg each week until good control is achieved.	6–10 h

Table 1 (*continued*)

Active Ingredient	Drug Name	Dosing	Duration of Behavioral Effects
Methylphenidate	Ritalin Tablets (scored): 5, 10, 20 mg Methylin Chewable tablets: 5, 10, 20 mg Methylin Oral solution: 5, 10 mg/5 mL	Start with 5 mg 1–2 times/d and increase by 5 mg each week until good control is achieved. May need third reduced dose in afternoon/evening. Maximum recommended dose: 60 mg	
	Focalin Tablets (scored): 2.5, 5, 10 mg	Start with 2.5 mg 1–2 times/d and increase by 2.5 mg each week until good control is achieved. May need third reduced dose in afternoon/evening. Maximum recommended dose: 30 mg	4–5 h
	Ritalin LA Capsule (can be sprinkled): 10, 20, 30, 40 mg Ritalin SR Tablet: 20 mg SR Metadate ER Extended-release tablet: 10, 20 mg Methylin ER Extended-release tablet: 10 mg Metadate CD Extended-release capsule (can be sprinkled): 10, 20, 30 mg	Start with 10–20 mg in morning and increase each week until good control is achieved. Alternatively, titrate using short-acting methylphenidate and then switch over to a longer-acting form. May need second dose or regular methylphenidate dose in afternoon/evening. Maximum recommended dose: 60 mg	6–10 h

Table 1 (*continued*)

Active Ingredient	Drug Name	Dosing	Duration of Behavioral Effects
Methylphenidate (*continued*)	Focalin XR Capsule (can be sprinkled): 5, 10, 20 mg	Start with 5 mg in morning and increase by 5 mg each week until good control is achieved. Maximum recommended dose: 30 mg	8–10 h
	Concerta Capsule (noncrushable): 18, 27, 36, 54 mg	Start at 18 mg in morning and increase by 18 mg each week until good control is achieved. Maximum recommended dose: 72 mg	8–12 h
	Daytrana Patch: 1.1, 1.8, 2.2, 3 mg/h	Worn daily for 9 hours. Patch to be replaced once a day in the morning. Skin sensitization as compared to contact rash may occur rarely, causing FDA advisory board to recommend oral methylphenidate use prior to the patch.	About 12 h
	Quillivant XR Liquid: 25 mg/5 mL	Start at 20 mg in morning and increase by 10–20 mg increments until good control is achieved. Before administering dose, vigorously shake the bottle for at least 10 seconds to ensure the proper dose is administered. Maximum recommended dose: 60 mg	

Abbreviation: FDA, US Food and Drug Administration.

Table 2. Additional Medications for Treatment of Attention-Deficit/Hyperactivity Disorder

Drug	Form	Dosing	Common Side Effects	Duration of Behavioral Effects	Benefits	Precautions
α-Agonists						
Catapres (clonidine HCL)	Tablets: 0.1, 0.2, 0.3 mg Patches TTS-1 TTS-2 TTS-3 Cream (by special order)	Start with 0.01–0.05 mg orally at night. May increase by 0.01–0.05 mg/d every 3–7 days up to 0.2–0.4 mg/d depending on weight; total dose may be divided into 3–4 doses.	Sleepiness, irritability, hypotension, dizziness, dry mouth, constipation, localized skin reactions with patch	Tablet: 3–6 h Patch: 1–5 d	Helpful for ADHD patients with significant comorbid tics; may be helpful for ADHD patients with aggression or insomnia	Sudden discontinuation could result in rebound hypertension; to avoid daytime tiredness, starting dose should be given at bedtime and increased slowly.
Kapvay (clonidine)	Extended-release tablets: 0.1, 0.2 mg	Start with 0.1-mg tablet at bedtime. Can add in second dose with breakfast. Dose should be given twice daily with an equal or higher split dosage being given at bedtime. Dosages >0.4 mg/d not evaluated in trials.	Sleepiness, irritability, hypotension, dizziness, dry mouth, constipation	12–24 h	May be helpful for ADHD patients as monotherapy or as an adjuvant therapy	Sudden discontinuation could result in rebound hypertension. To avoid daytime tiredness when discontinuing, the total dose should be tapered in decrements of no more than 0.1 mg every 3–7 days.

Table 2 (*continued*)

Drug	Form	Dosing	Common Side Effects	Duration of Behavioral Effects	Benefits	Precautions
Tenex (guanfacine)	Tablets: 1, 2 mg	Start with 0.5 mg orally at night. Increase by 0.5 mg/d every week up to 2–4 mg/d (≥45 kg) depending on weight; total dose may be divided into 2–4 doses/d.	Irritability, tiredness, confusion at higher doses, agitation	About 24 hours in the body, but must be taken 2 (or 3) times/d.	May be helpful for ADHD patients with aggression. Causes less sedation and irritability than clonidine.	Sudden discontinuation could result in rebound hypertension; to avoid daytime tiredness, starting dose given at bedtime and increased slowly.
Intuniv (guanfacine)	Extended-release tablets: 1, 2, 3, 4 mg	Start with 1 mg and increase by no more than 1 mg/wk. Maintain dose in range of 1–4 mg/d.	Irritability, tiredness, confusion at higher doses, agitation	24 h	May be helpful for ADHD patients as monotherapy or as an adjuvant therapy. Causes less sedation and irritability than clonidine.	Sudden discontinuation could result in rebound hypertension; to avoid daytime tiredness, starting dose given at bedtime and increased slowly.
Atypical Antidepressants						
Wellbutrin (bupropion)	Tablets: 75, 100 mg Sustained-release tablets: 100, 150, 200 mg Extended-release (XL): 150, 300 mg	Start with 75 mg given twice/d; sustained release can be given in 1–2 doses. Maximum 450 mg/d.	Irritability, decreased appetite, insomnia, worsening tics, seizures, rash	8–24 hours, depending on formulation	Helpful as second-line treatment for ADHD or for ADHD patients with comorbid anxiety or depression	Contraindicated in patients with a history of seizures or eating disorders. May increase risk of suicidality.

Table 2 (*continued*)

Drug	Form	Dosing	Common Side Effects	Duration of Behavioral Effects	Benefits	Precautions
Selective Norepinephrine Reuptake Inhibitors						
Strattera (atomoxetine)	Capsules: 10, 18, 25, 40, 60, 80, 100 mg	Start with a dose of 0.5 mg/kg orally in the morning for at least 3 days. May increase to 1.4 mg/kg/d or 100 mg/d, whichever is less; total dose may be divided into 1–2 doses/d.	Nausea, vomiting, fatigue, decreased appetite, dizziness, aggression, tiredness, constipation, dry mouth, insomnia, decreased libido, mood swings	18–24 h	Helpful as second-line treatment for ADHD or for ADHD patients with comorbid anxiety	May increase risk of suicidality. Should not be used within 2 weeks of a monamine oxidase inhibitor or in a patient with narrow-angle glaucoma.

Abbreviation: ADHD, attention-deficit/hyperactivity disorder.

- Warnings have surfaced about aggression, suicidality, reversible hepatotoxicity, and cardiac effects.

- Tricyclic antidepressants (desipramine, nortriptyline)
  - Low toxic to therapeutic ratio has virtually eliminated their use in children with ADHD.
- Atypical antidepressants (bupropion)
  - Suggested as an option in youth with comorbid depression
- α-Agonists (clonidine and guanfacine)
  - Moderate effects on hyperactivity and impulsivity, aggression, and tics.
  - Given their effect on the cardiovascular system, care must be taken to avoid stopping these medications abruptly, which might result in rebound hypertension.
  - Sedation, particularly with clonidine, can be a significant problem.

Management of Side Effects

- General
  - For mild side effects, allow 7–10 days for tolerance to develop.
  - Evaluate action time and determine whether timing of administration can be adjusted to minimize side effects.
  - Determine whether side effects are related to other disorders or current environmental stressors and adjust accordingly.
  - If these strategies fail, consider an alternative stimulant.
- Weight loss or anorexia
  - Administer medication during or after a meal.
  - Try calorie enhancement strategies, such as high-protein instant breakfasts or protein bars.
  - Get eating started with any highly preferred food before giving regular foods.
  - Allow grazing in the evening when appetite suppression wanes.
  - Change stimulant medications.
  - Consider drug holidays.
- Dizziness
  - Monitor blood pressure and pulse.
  - Encourage adequate hydration.
  - If dizziness is associated only with peak drug effect, try a longer-acting preparation.
- Insomnia or nightmares
  - Establish bedtime routine.
  - Omit or reduce the last dose or change to the standard, short-acting version if the patient is using longer-acting preparation.

- Administer medication earlier in the day.
- Try a different stimulant.
- Consider additional medication as a last resort.

- Dysphoric mood/emotional constriction
  - If the problem occurs during peak drug effect, reduce the dose or switch to a longer-acting preparation.
  - Evaluate when it occurs.
  - Try a different stimulant.
  - Consider comorbid anxiety or depression disorders requiring alternative or adjunct treatment.
  - Consider additional medication as a last resort.
- Rebound
  - Try to decrease precipitous drop in blood levels by
    - Using a stepped-down dose at the end of the day
    - Increasing morning long-acting dose
    - Adding a smaller dose of short-acting medication toward the end of the day
  - Switch to a longer-acting preparation.
  - Combine longer-acting and short-acting preparations.
  - Overlap stimulant dosing.
- Tics
  - Conduct drug trial at different doses, including no medication, to be sure that tics are drug related.
  - For mild tics that abate after 7–10 days, reconsider risk versus benefit and negotiate a new informed consent with the parent or guardian.
  - Conduct a drug trial to see whether tics abate with another stimulant.
  - Consider a non-stimulant treatment, such as clonidine, alone or in combination with a stimulant.
  - Refer to a mental health specialist or neurologist skilled in the management of tics.
  - If tics appear suddenly after a sore throat or sinus infection, consider strep-associated tics or PANDAS (**p**ediatric **a**utoimmune **n**eurologic **d**isorders **a**ssociated with **s**trep) and treat with appropriate antibiotic.
- Psychosis
  - Check that correct dose is being administered.
  - Discontinue stimulant treatment.
  - Assess for presence of coexisting bipolar or thought disorder.
  - Consider alternative treatments or referral to mental health specialist.

Behavioral Techniques

- Use of behavioral techniques in combination with medication may allow reduction of medication dose.
- Therapeutic benefits of stimulant medication usually occur during the day, whereas behavioral interventions may be used in late afternoon or evening in place of an additional dose of medication.
- Disruptive disorders that commonly co-occur with ADHD have been shown to respond to behavioral modification.
- Psychosocial treatment may help to enhance parents' positive perception of their children and of their own parenting abilities.
- Results for medication last only as long as a youth continues to take the medication, whereas behavioral interventions may extend over time.
- Medications may be more expensive than behavioral interventions in the long run.
- Specific techniques include
  - Positive reinforcement
    - Provide rewards or privileges contingent on the child's performance.
  - Time-out
    - Remove access to positive reinforcement contingent on performance of unwanted or problem behavior.
  - Response cost
    - Withdraw rewards or privileges contingent on the performance of unwanted or problem behavior.
  - Token economy
    - Combine positive reinforcement and response cost.
    - The child earns rewards and privileges contingent on performing desired behaviors and loses rewards and privileges based on undesirable behavior (eg, working toward a prize).

WHEN TO ADMIT

- The core symptoms of ADHD should not necessitate admission to a medical or psychiatric hospital.
- Indications for admission include
  - Symptoms related to mental health conditions that may co-occur with ADHD
  - Adverse event secondary to medication used to treat ADHD
  - A medical condition resulting from the core symptoms of inattention, hyperactivity, or impulsivity associated with ADHD (eg, accidental injury)

WHEN TO REFER

- Refer to a mental health or school-based professional if
  - A comorbid condition is suspected.
  - A clinician is not equipped to evaluate sufficiently for these types of disorders in the office setting.
  - Results of assessment are discrepant or a complicated clinical picture exists and the primary care physician is uncomfortable continuing evaluation.
  - Psychological testing is needed.
  - Intensive parent training in behavior modification is needed.
  - Pharmacologic management of treatment-resistant ADHD is needed or severe side effects occur.
  - Major depressive disorder requires immediate referral before initiating treatment for ADHD.
  - Coexisting conditions that are unresponsive to treatment for ADHD are present (oppositionality, depression, and anxiety may improve with treatment of ADHD core symptoms).
    - Psychosocial or pharmacologic interventions for a coexisting mental health disorder
    - Significant familial stress or psychopathology
      - Domestic violence
      - Substance use disorder
- A mental health resource list can help identify local mental health care professionals on the family's insurance plan who can evaluate the youth for possible comorbid mental health disorders.
- Bright Futures provides a template for mental health referrals that can be used to structure referral information.
- For school referrals, parents should be directed to draft a letter requesting a multidisciplinary evaluation, including psychoeducational testing, if the history suggests a possible learning disability, such as
  - Reading disorder (dyslexia)
  - Mathematics disorder (dyscalculia)
  - Disorder of written expression
  - Communication disorder
- Public schools are required to respond to family requests for evaluations within a specified period (determined by school district policies).
- Children attending private schools or those who are homeschooled are eligible to receive an evaluation through their local school district.
- Families may be referred to independent psychologists for psychoeducational evaluations through their insurance plans.
  - Clinicians should inquire whether the local school district accepts outside evaluations before making any referrals.

FOLLOW-UP

- Youth functioning should be systematically monitored over time to evaluate whether target outcomes are achieved or adverse side effects to treatment develop.
  - If targeted outcomes are not met, the clinician, parents, and school personnel should collaboratively determine
    - Validity of the diagnosis
    - Adherence to all components of the treatment plan
    - Possibility of previously unidentified coexisting conditions
  - The AAP ADHD toolkit includes sample management plans and follow-up assessment forms to assist clinicians in monitoring treatment.
- Once a child is stable on a medication, AAP treatment guidelines recommend an office visit every 3–6 months to reassess
  - Academic performance
  - Behavior
  - Side effects
- More intensive visits may be necessary around predictable periods of change.
  - Entry into middle or high school
  - Onset of puberty
- Trials off medication are important to conduct but should be scheduled so as to not overlap with
  - Beginning of school terms
  - Examinations
  - Family stressors
- Families, youth, and clinicians should consider carefully using medication in the afternoons and evenings, on weekends, and during the summer.

- Take into account
  - Severity of a youth's dysfunction
  - Effect on family and peers
  - Cultural expectations
  - Any decrease in weight or height velocity

- School-based services
  - Youth can access school-based services through the local public school system.
    - Individual teachers will often modify curriculum or classroom environment to address a child's needs.
    - Many schools have an interdisciplinary council (eg, student study team, multidisciplinary assessment team) that informally reviews a child's academic performance and behavior and suggests possible remediation.
    - Through Section 504 of the Rehabilitation Act, school systems are mandated to provide accommodations in the mainstream classroom.
    - Under IDEA, school systems provide a continuum of special education services, ranging from accommodations in the mainstream classroom to a special day class in a public or private, nonpublic placement.
    - Youth with ADHD often qualify for special education services because of a coexisting specific learning disability, language disorder, or severe emotional disturbance.
      - Organizational difficulties may require
        - Supervision of the writing of homework assignments in a planner
        - Extra set of books at home
        - Assistance breaking large projects into small steps
      - Approaches to problems with handwriting
        - Access to a computer for written work
        - Copies of teacher lectures
        - Electronically recorded textbooks
    - If behavior interferes with the child's academic performance or the ability of other children in the classroom to learn, a behavioral intervention plan that delineates the following items is necessary:
      - What behaviors a youth displays
      - Factors that escalate or dampen the behavior
      - Appropriate behavioral interventions
  - Consideration should be given to the appropriate educational placement of a child.
    - Mainstream classroom with or without assistance from a resource specialist
    - Special day class
    - Private, nonpublic placement
  - Sample letters requesting a 504 plan or IEP, as well as additional information on these programs, are available in the AAP ADHD toolkit and on the Bright Futures Web site (http://brightfutures.aap.org).
  - Concerns exist that these accommodations may lead to youth who feel entitled to extra assistance and will not be able to function adequately in college or the workplace setting.
    - Accommodations must be provided within the context of teaching the child to understand his or her own strengths and weaknesses.
    - The child needs to develop compensatory strategies for addressing areas of challenge.

PROGNOSIS

- Youths with ADHD who have been monitored into adolescence demonstrated increased risk for
  - Poor academic attainment
  - Impaired familial and peer functioning
  - Lower self-esteem
  - Substance use disorder
  - Delinquency
  - Driving-related accidents
- Treatment may ameliorate some risks, particularly for substance use disorder.
- Age-dependent decline appears to exist in apparent symptoms as children grow older.
  - Hyperactivity and impulsivity tend to remit at a greater rate than inattention.
- As many as 70% of children and adolescents continue to be symptomatic in adulthood, but outcomes are improved with
  - Familial stability and support
  - Ongoing therapeutic relationships with a health care professional
  - Higher IQ

DEFINITION

- Autism spectrum disorder (ASD) is a neurobiological developmental disorder characterized by
  - Significant developmental delays in language and communication skills
  - Abnormalities in language when it does develop
  - Significant impairments in reciprocal social behavior
  - Narrow repertoire of interests and behaviors
  - Ritualized and repetitive behavior patterns
  - Stereotyped, destructive, and disruptive behavior problems

SIGNS AND SYMPTOMS

History

- Medical history
  - Birth and neonatal history
  - History of seizures
  - Hyperactivity (extreme)
  - Pica
  - Family history of ASD or intellectual disability
- Developmental history
  - Delayed milestones
  - Regression in development
  - Delays in language and social development
  - Learning difficulties
  - Intellectual disability
- Psychosocial history
  - Excessive irritability
  - Self-injury
  - Frequently, feeding or sleeping problems
  - Mental health problems
  - Social difficulties

Physical Examination

- Head circumference.
  - Sometimes larger in early childhood than in typically developing children
- Motor impairments may include
  - Hand flapping
  - Hypotonia
  - Limb apraxia
    - Hypotonia and limb apraxia are more common among children with isolated intellectual disability and other developmental disabilities than among children with ASD.
- Rule out hearing impairment.
  - Young children with hearing problems often present with language delays and even some repetitive behavior (eg, shaking their heads back and forth).
- Rule out tuberous sclerosis.
  - Neurocutaneous disorder affecting the brain and other organs

Screening and Evaluation—Standardized Instruments

- The American Academy of Pediatrics (AAP) recommends that primary care physicians screen for developmental concerns at every well-child preventive care visit.
- If concerns are raised
  - Complete a standardized developmental screening test to determine if further evaluation is necessary.
  - Standardized screening tests for developmental delays should also be administered at the 9-, 18-, and 24- or 30-month visits.
- AAP guidelines recommend that an ASD-specific tool should be administered to all children at the 18- and 24- or 30-month visits.
- Modified Checklist for Autism in Toddlers (M-CHAT).
  - For children 18–30 months old
  - Widely used for screening
  - Lacks specificity as a diagnostic measure
  - High false-positive rate
    - A structured follow-up interview is available to better identify those in need of further evaluation.

DIFFERENTIAL DIAGNOSIS

- *Diagnostic and Statistical Manual of Mental Disorders,* 5th Edition (*DSM-5*) now includes 4 previously separate diagnoses under the term *ASD.*
  - Autistic disorder
  - Asperger disorder
  - Pervasive developmental disorder not otherwise specified (PDD-NOS)
  - Childhood disintegrative disorder
- Under *DSM-5*
  - Children must meet the criteria for all 3 social and communication deficits for ASD.
  - They must also exhibit ≥2 symptoms under the category of restricted, repetitive behaviors.
  - Individuals diagnosed under *DSM-IV* criteria do not need to be rediagnosed, so available services should not change for previously diagnosed children.

A

- ASD.
  - Autistic disorder
    - Child meets full diagnostic criteria for
      - Language (delayed or impaired)
      - Social interaction (impaired)
      - Repetitive, restricted behaviors
  - Asperger disorder
    - Typical language development
    - Impaired social interactions
    - Repetitive, restricted behaviors
  - PDD-NOS
    - Language delays, impaired social interaction, or restricted, repetitive behaviors.
    - Symptoms are not present to the degree that would warrant a more specific diagnosis.
- Pervasive developmental disorders that are not ASD include
  - Childhood disintegrative disorder
    - A period of developmental regression after ≥2 years of normal development
  - Rett syndrome
    - *DSM-5* considers Rett syndrome to be a separate diagnosis from ASD because of the specific genetic etiology of Rett syndrome.
    - Deceleration of head growth.
    - Loss of purposeful hand movements.
    - Stereotyped hand movements (hand wringing or mouthing).
    - Gait abnormalities.
    - Severe to profound language and cognitive delays.
    - Mutations of the *MECP2* gene on the X chromosome.
      - More common in girls than boys
  - Developmental language disorder
    - Delays in receptive or expressive language skills (or both).
    - Social interaction skills are not impaired.
      - Children with developmental language disorders may exhibit social deficits because of their inability to maintain social interactions involving language.
    - No demonstration of repetitive, restricted behaviors.
- Tuberous sclerosis.
  - Neurocutaneous disorder that affects the brain and other organs.
  - Can account for 0.4%–3.0% of children diagnosed with ASD.
  - 2 gene loci.
  - Most common initial signs are ash leaf–shaped depigmented macules observed with exposure to UV light.
    - Any child being assessed for ASD should be exposed to UV light to exclude tuberous sclerosis.
    - If the assessment result is positive, the child should be referred to a geneticist.

DIAGNOSTIC APPROACH

- Diagnosis is not straightforward.
  - No single biological marker, laboratory test, or procedure to identify ASD
- Primarily a behavioral diagnosis, based on
  - Comprehensive history
  - Direct observation
  - Standardized assessment
- Comorbid conditions with ASD include
  - Intellectual disability
    - Reported in ~70% of children with ASD
  - Seizures
  - Gastrointestinal problems
  - Sleep difficulties
  - Behavioral problems
    - Pica
    - Self-injury
    - Aggression

LABORATORY FINDINGS

- Genetic consultation is recommended for all children given a diagnosis of ASD.
  - High rates of heritability.
  - Research increasingly links the occurrence of ASD with epigenetic factors.
- Families should be offered
  - A microarray that tests for developmentally significant regions of the genome and for common genetic syndromes
  - A DNA study for fragile X syndrome
- Genetic testing will not change the treatment for specific ASD symptoms, but results may
  - Establish etiology for current symptoms.
  - Help the family better understand the risk of recurrence in siblings.
  - Help identify potential medical concerns associated with specific genetic syndromes.

- Specific testing should be considered for
  - *PTEN* gene mutation when head circumference is >2.5 SDs above the mean
  - *MECP2* gene mutation
    - To rule out Rett syndrome and related phenotypes when a patient presents with microcephaly, deceleration of head growth, developmental regression, or stereotypical "hand-wringing" movements
  - Angelman syndrome
    - When seizure disorder is present along with symptoms of ASD in early childhood
    - Intellectual disability, very happy affect, and repetitive hand waving/clapping
- Lead screening.
  - Pica is a common comorbidity associated with lead toxicity.
- Metabolic and genetic testing should be considered in children with
  - Unusual and dysmorphic features
  - Seizures
  - Abnormal growth

IMAGING

- No imaging evaluation procedures are needed in routine evaluation for ASD.
- Standard assessment should be considered in children with co-occurring neurologic findings, including
  - Seizures
  - Asymmetric motor functioning
  - Cranial nerve dysfunction
  - Severe headache

DIAGNOSTIC PROCEDURES

- Electrophysiologic testing is needed only in patients with
  - Suspected seizure disorder
  - Severe sleep problems
  - Developmental regression

TREATMENT APPROACH

- General approach for managing ASD
  - Screen to identify children at risk.
  - Refer to a specialist for evaluation.
  - Manage medical comorbidities.
  - Prescribe and manage psychopharmacologic medications.
  - Refer for psychosocial interventions.
  - Coordinate specialty services and referrals.
- Medical home model of care
  - Helps to ensure that children receive needed preventive care and access to specialty services in a timely manner
  - Helps avoid duplicating services by improving care coordination and communication between health care professionals

SPECIFIC TREATMENTS

Psychopharmacologic Treatment

- No medications currently are approved to treat core symptoms (eg, social/communication deficits, restricted/repetitive behaviors), although there is evidence that commonly associated behavioral problems can be partially managed with medication.
- Symptoms of attention-deficit/hyperactivity disorder (ADHD) often are seen in children with ASD, and *DSM-5* allows both diagnoses to be given together.
  - Symptoms of hyperactivity, impulsivity, and inattention should be carefully evaluated using current accepted standards.
    - Evaluate whether symptoms significantly affect functioning across environments (eg, school, home).
    - Rule out other possible causes for symptoms (eg, sleep problems, constipation/gastrointestinal problems, anxiety/depression).
  - If the child meets criteria for comorbid ADHD, help the family connect with additional services (eg, school, mental health professionals) for appropriate behavioral and academic interventions.
  - After interventions have been put into place, reevaluate severity of ADHD symptoms on everyday functioning to determine if a trial of medication is necessary.
  - Physicians should then follow recommended guidelines for medication selection.
- Stimulant medications (eg, methylphenidate and amphetamine preparations) are most often prescribed as the first-line choice for comorbid ADHD.
  - Initial research indicates that the rate of therapeutic response may be lower and the rate of side effects (particularly irritability) may be higher in children with both ASD and ADHD than in children with only a diagnosis of ADHD.

- Atomoxetine and α_2-agonists (eg, guanfacine and clonidine) may be effective in reducing ADHD symptoms.
  - Research on effectiveness and side effects has been limited, particularly in an ASD.
- Risperidone and aripiprazole currently are the only medications approved by the US Food and Drug Administration for treating behavioral problems in ASD.
  - Both have been shown to be effective in reducing irritability, aggression, self-injury, stereotypy, and hyperactivity in some children with ASD.
  - They are associated with several significant side effects, including increased weight gain, sedation, and risk of extrapyramidal symptoms.
- Selective serotonin reuptake inhibitors (eg, fluoxetine, sertraline)
  - Have not been found to improve repetitive behaviors
  - Have been frequently associated with adverse effects in children with ASD
- Long-term effects of any of these medications on the neurophysiologic development of young children have not been determined.

Psychosocial Interventions

- Early intensive behavioral intervention
  - Age 2–7 years
  - Intensive (20–40 hours per week)
  - Based on principles of applied behavior analysis
- Programs ideally offered for
  - ≥2 years
  - 40 hours per week
  - One-on-one behavioral instruction
  - The literature is mixed, but targeted outcomes include
    - Age-level functioning
    - Normal intelligence
    - Average adaptive behavior
    - Regular educational placement

Speech and Occupational Therapies

- Speech and occupational therapies are indicated for most children with ASD.
  - Often provided through child's individualized education program (IEP).
  - Recommend that families access these services privately to maximize intervention time and to develop plans that can be implemented specifically in the home environment.
- Older children with better language skills may benefit from evidence-based social skills training focused on pragmatic language skills for effective communication and interaction with peers and adults.

WHEN TO ADMIT

- Severe malnutrition related to feeding difficulties
- Severe seizures
- Long-term electroencephalogram (EEG) monitoring
- Life-threatening self-injurious behavior or aggression
- Psychopharmacologic toxicity
- Psychiatric stabilization

WHEN TO REFER

- Refer to a developmental specialist if any of the following criteria are present in child 12–24 months of age:
  - Delays in expressive communication: lack of babbling by 12 months, single words by 18 months, or phrases (not just echoed language) by 24 months
  - Inability to follow simple instructions or imitate others by 12 months
  - Little interest in social games by 12 months
  - Little eye contact or social smiling by 12 months
  - Lack of pointing out objects of interest by 18 months
  - Inability to direct the child's attention or lack of response to name by 18 months
  - No simple pretend play (eg, feeding a doll) by 18 months
  - Little interest in other children by 24 months
  - Loss of language or social skills at any age
  - Repetitive motor movements or atypical body posturing (eg, hand flapping, body or facial tensing)
  - For child <3 years, refer to early intervention services.
  - For child ≥3 years, refer to developmental disability services.
- Children with a diagnosis of ASD may need referral for further evaluation and treatment for common comorbid conditions.
  - Seizures
    - EEG to evaluate seizure activity
    - Neurologist for further evaluation and medication

- Sleep disorders
  - Sleep specialist
  - Neurologist
  - Ear, nose, and throat specialist
- Gastrointestinal concerns (eg, severe constipation, food allergies, malnutrition)
- Feeding difficulties
  - Psychologist/behavior specialist for feeding therapy if problem is behavioral.
  - Speech/occupational therapist for feeding therapy if problem is related to oral motor deficits.
  - If outpatient therapy is unsuccessful, consider referral to an inpatient feeding clinic.
- Pica
  - Behavior therapy to develop a plan with family
- Toilet training difficulties
  - Psychologist or behavior specialist to create and help implement an intervention plan for families
- Motor delays
  - Occupational therapy evaluation to evaluate and treat fine motor deficits
  - Physical therapy evaluation to evaluate and treat gross motor deficits
- Significant behavior problems (eg, aggression, self-injury, noncompliance)
- Mental health concerns (eg, significant anxiety or depression)

PROGNOSIS

- Prognosis has improved over the past 3 decades.
- For children with developmental disabilities
  - Increased availability of community special education services
  - Decreased institutionalization
  - Increased access to learning experiences
- Children with ASD and intellectual disability have the poorest prognosis.
- Parents, teachers, and health professionals have learned to advocate for children with developmental disabilities.
- Advances in epigenetics will likely shed light on the various causes of ASD and, thereby, provide prevention options.

Back Pain

DEFINITION

- Pain or discomfort in the region from the upper thoracic vertebra (T1) and shoulder girdle to the sacrum and surrounding musculature.
- Patients may have a specific sense of localization (eg, to a muscle group or vertebral body) or sense the pain as diffuse or deep and difficult to localize.

HISTORY

History should ascertain

- Description of pain: OLDCAR.
  - **O**nset/precipitating event (eg, trauma)
  - **L**ocation (eg, midline, paraspinal)
  - **D**uration
  - **C**haracteristics, nature, or quality (continuous or not, severity, whether present when awakening from sleep)
  - **A**ssociated factors which improve or worsen (eg, activity)
  - **R**adiating pattern of pain
- Changes in urination or defecation.
- Other related neurologic findings.
- Whether fever is present.
  - Exposures to infectious agents (eg, tuberculosis)
  - Signs of systemic illness
    - Weight loss
    - Bone pain in other locations
    - Bruising
    - Organomegaly
    - Adenopathy
- Specific activities, especially those that require spinal extension (gymnastics, football); history of training.
- Changes in activities, such as walking, play, and sports activities.
- Growth patterns/recent growth spurt.
- Consider an evaluation of family and social factors if functional pain is in the differential diagnosis.
- Special considerations include
  - Confirm pain history with others (eg, parents, coaches, school personnel).
  - Children may minimize pain because of fear of procedures.
  - Children and adolescents usually do not use pain symptoms for secondary gain.

PHYSICAL EXAMINATION

Physical Examination Considerations

- Vital signs
  - Temperature (febrile or not).
  - Pain may elevate heart rate and blood pressure.
- Spinal examination
  - Palpate for step-offs.
  - See whether there is midline or paraspinal tenderness.
  - Straight leg raising test.
    - A positive result is highly suggestive of nerve root compression.
    - Using cervical flexion to accentuate the patient's symptoms may add to the test's sensitivity.
    - Any reproduction of the patient's usual symptoms during testing before 60° of hip flexion, or marked asymmetry, should be considered a positive result.
    - Pain after 60° or limited to the posterior thigh is more likely caused by hamstring tightness.
  - May evaluate for scoliosis.
    - Idiopathic scoliosis is not causally tied to pain in children.
    - With scoliosis and pain, consider an alternative cause.
  - In case of trauma, check airway, breathing, and circulation; cervical spine; ribs; and pelvic stability and implement cervical spine and other precautions as needed.
- Neurologic evaluation for the following conditions at or below the suspected level of the lesion:
  - Motor function (including symmetry, strength, gait, and coordination)
  - Sensation
  - Reflexes
  - Rectal sphincter tone
- Evaluate the skin for evidence of bruising or trauma.
- Check for the presence of organomegaly or lymphadenopathy.

Physical Considerations Particular to Adolescents

- Look for excessive lordotic curvature, especially in children who perform repetitive spinal extension (eg, gymnasts, football linemen).
- Look for evidence of connective tissue disorders.
  - Hyperextensibility
  - Marfanoid body habitus
    - Joint hyperextensibility
    - Pectus excavatum
    - Pes planus
    - Dislocated lenses
    - Hernia
    - Arachnodactyly
    - Scoliosis
- Stork test: Can pain be reproduced reliably by hyperextension of back while standing on one leg?
- Waddell signs: Presence of ≥3 of the following 5 criteria may help determine whether significant psychological stress is associated with chronic low back pain:
  - Inappropriate tenderness that is superficial or widespread
  - Pain on pressing the top of the head or on passive rotation of shoulders and pelvis
  - Distraction signs, such as inconsistent performance between straight leg raising in the seated and supine positions
  - Strength and sensory loss patterns that do not fit with accepted neuroanatomy
  - Overreaction during the physical examination

DIFFERENTIAL DIAGNOSIS

All Children

- Back pain before adolescence is uncommon.
- Be aware of the relatively higher risk of serious underlying disease in younger children, even those without specific physical findings.
- The combination of fever and back pain strongly suggests an infectious, inflammatory, or neoplastic process in all age groups.
- Fever in the setting of the following conditions should prompt aggressive diagnostic evaluation for cancer:
  - Weight loss
  - Bone pain in other locations
  - Bruising
  - Organomegaly
  - Adenopathy
- Neurologic symptoms along with back pain may indicate lumbar disk herniation or other nerve compression.
- Idiopathic scoliosis usually does not cause back pain in children.
  - Scoliosis with pain should raise concern for another cause, eg, spinal malignancy, osteoid osteoma.

Newborns, Infants, and Young Children (Through Third or Fourth Year of Life)

- Infants and toddlers are not always capable of localizing or complaining about pain in the back.
- Differential diagnosis includes
  - Diskitis
    - Unexplained fever or toxicity *and*
    - Refusal to walk or stand
  - Leukemia
  - Lymphoma
  - Vasoocclusive crisis
  - Vertebral osteomyelitis/epidural abscess, in a child with sickle cell disease
  - Trauma (especially intentional injury)
  - Pyelonephritis

Children (0–21 years)

- Pyelonephritis.
  - Consider with fever; costovertebral angle tenderness; dysuria; polyuria; urinary urgency; or cloudy, dark, or pink/red-tinged urine.
- Diskitis.
  - Unusual, if not rare, condition.
  - Most common in children <10 years.
  - Typical discomfort in an upright posture.
  - Refusal to walk or pain when bending forward.
  - Even in the absence of fever, a child (especially preschool age) who refuses to walk should be evaluated for diskitis.
- Tethered cord.
  - Back pain when walking may be the only sign at presentation.
  - Sacral dimple of unclear depth, hairy patch, or discoloration.
  - Bowel or bladder issues.
  - Lower extremity weakness.
- Vertebral osteomyelitis.
  - Usually affects school-aged children and teenagers
  - Causes severe back pain and systemic symptoms
- Ankylosing spondylitis.
  - Consider with a family history of rheumatoid disease.
- Vasoocclusive crisis.
  - Consider in patients with sickle cell disease.
- Leukemia, lymphoma.

- Primary vertebral tumors.
  - Ewing sarcoma
  - Aneurysmal bone cyst
  - Benign osteoblastoma
  - Osteoid osteoma
- Spinal tuberculosis (Pott disease).
  - Rare in US children; mainly occurs in children in regions where tuberculosis is endemic.
  - Consider if back pain is accompanied by low-grade fever.
- Underlying leg-length discrepancy may result in chronic or recurrent low-back pain from musculoligamentous strain.

Adolescents

Acute Pain (<3 Weeks)

- Lumbar disk disease
- Apophyseal ring fractures
- Muscular or ligamentous strain
  - Lower back pain ≤3 weeks' duration
  - With or without recollection of injury
  - Pain exacerbated by lifting, stooping, or exercising
  - May be caused by repetitive strain coupled with genetic predisposition and environmental factors, such as
    - — Prolonged seated posture and bending forward, as with studying or reading while sitting at a desk
    - — Carrying an excessively heavy backpack (10%–20% of body weight)
- Sciatica/piriformis syndrome
- Vertebral osteomyelitis
- Epidural abscess
- Spinal tuberculosis
- Pyelonephritis
  - Consider with fever, costovertebral angle tenderness, dysuria, polyuria, urinary urgency, or cloudy, dark, or pink/red-tinged urine.

Chronic Pain (≥3 Weeks)

- Spondylolysis
  - A defect, most commonly a stress fracture, of the pars interarticularis.
  - One of the most common identifiable causes of low-back pain in this age group.
  - Athletes participating in gymnastics, dance, cheerleading, football, and diving are at highest risk.
  - Individuals with benign hypermobility syndrome may be at risk.
- Spondylolisthesis (anterior movement of vertebral body on top of another, usually L5 on S1)
  - A result of bilateral spondylolysis
  - One of the most common identifiable causes of low-back pain in this age group
- Scheuermann kyphosis (thoracolumbar spinal deformity with localized vertebral body changes)
- Facet or vertebral dysfunction
- Sacroiliac dysfunction
- Lumbar disk disease
  - Especially in athletes or others with cumulative trauma
- Spinal stenosis
- Ankylosing spondylitis (spondyloarthropathy of the spine)
  - Should be suspected with
    - — Limited lumbar flexion (modified Schober test)
    - — Tenderness at entheses (particularly the Achilles-calcaneal enthesis), origin or insertion of plantar fascia, sacroiliac joints, or base of the fifth metatarsal
    - — Pain in sacroiliac joints with flexion-abduction and external rotation (abnormal FABER [**f**lexion, **ab**duction, and **e**xternal **r**otation] test)
- Tumor or cancer
  - Osteoid osteoma and osteoblastoma
    - — Consider in cases of nocturnal back pain, even if relieved by nonprescription analgesics.
- Prolonged muscular or ligamentous strain
- Functional (nonorganic) pain

LABORATORY EVALUATION

- History and physical examination often suffice.
- When appropriate for differential diagnosis, consider
  - Complete blood cell count
  - Erythrocyte sedimentation rate
  - Urinalysis and culture (if considering nephrolithiasis, urine calcium and creatinine)
  - Uric acid
  - Lactate dehydrogenase

IMAGING

Imaging is guided by clinical suspicion; options include

- Radiographs of the spine (anteroposterior [AP], lateral, oblique views)
- Computed tomography (CT)
- Magnetic resonance imaging (MRI)
- Nuclear medicine imaging (bone scans)
- Single-photon emission computed tomography (SPECT)

By suspected diagnoses

- Muscle or ligament strain
  - Studies not routinely indicated
- Compression fracture (eg, after trauma such as motor vehicle accident, athletic injury)
  - Spinal radiography (AP, lateral)
- Diskitis
  - Spinal radiography
  - MRI as indicated
- Osteoid osteoma or osteoblastoma
  - Spinal radiography
    - Primary vertebral tumors almost always will be visible.
  - CT is the definitive study.
  - If radiography is inadequate, consider bone scan, CT, or MRI.
- Scheuermann disease
  - Spinal radiography (lateral)
    - Diagnosis is confirmed by anterior wedging of ≥3 contiguous vertebrae, by ≥5°.
  - Consider oblique views, as associated with spondylolysis.
- Spondylolysis
  - Spinal radiography (AP, lateral, oblique).
    - "Scottie dog with a collar" can be seen on the oblique view.
    - Normal radiography may not rule out the diagnosis.
  - Consider SPECT if the diagnosis is highly suggested.
  - A positive radiograph and negative SPECT results indicate that spondylolysis is not metabolically active (may not be the cause of back pain).
  - Back pain on extension with normal radiographs and positive SPECT results usually indicates facet or vertebral dysfunction.
- Spondylolisthesis
  - Spinal radiography (lateral)
    - Used to diagnose anterior slippage and to stage treatment
    - Rarely, may reveal congenital absence of a lumbosacral articular process
- Spondyloarthropathy (ankylosing spondylitis)
  - MRI with gadolinium of the sacroiliac joints and ultrasound of entheses can confirm local inflammation.

DIAGNOSTIC PROCEDURES

- In the case of vertebral osteomyelitis/epidural abscess, consider aspiration and culture.

TREATMENT APPROACH

- Consider whether pain is acute (<3 weeks) or chronic.
  - Acute pain, especially with a history of musculoskeletal injury, may be managed conservatively.
- Chronic pain demands further investigation.
- Back pain that results from an underlying disorder will probably require treatment of the primary condition, in addition to treatment of pain.
- Psychosocial or functional causes should be considered if
  - Thorough diagnostic evaluation of chronic back pain is unrevealing *and*
  - Usual management involving exercise and stretching is not beneficial.
- As children and adolescents usually do not use pain symptoms for secondary gain, do not assume that pain is feigned; rather, assume that it represents a very real physical symptom rooted in psychologic or emotional distress.
  - This distress can be addressed openly by the clinician.
  - After diagnosis, remember to reconsider nonfunctional causes, especially if symptoms continue to evolve.

SPECIFIC TREATMENT

Diskitis

- Treatment depends on cause.
- Most experts recommend
  - If bacterial cause, parenteral followed by oral antibiotics
  - Rest and pain management

Vertebral Osteomyelitis/Epidural Abscess

- Prompt orthopedic surgery consultation
- Antibiotics (ensure staphylococcal coverage)
- Rest and pain management

Ankylosing Spondylitis

- Best coordinated by a pediatric rheumatologist
- Anti-inflammatories
- Physical and occupational therapy

Vasoocclusive Crisis

- Careful evaluation and reassessment for acute chest syndrome and other related complications of sickle cell disease
- Hydration, red blood cell transfusion as indicated
- Pain management
- Physical therapy as indicated

Cancer, Including Leukemia, Lymphoma, Ewing Sarcoma

- Manage with a pediatric oncologist.

Osteoid Osteoma

- Nonsteroidal anti-inflammatory agents.
- Refer to pediatric orthopedic surgery for possible excision.

Musculoskeletal Back Pain

- For acute pain, think PRICEMMMS (**p**rotection, **r**est, **i**ce, **c**ompression, **e**levation, **m**edication, **m**otion, **m**odalities, strength).
- For chronic pain, heat may be helpful.
- Discourage bed rest, as this may delay recovery.
- Teach proper posture.
- Pain-free activity may be resumed gradually.
- Backpack weights should not exceed 10%–20% of the person's body weight.
- Exercise may be helpful.
  - Stretch after warming the muscles by gentle exercise.
    - — Improve flexibility of lower back and hamstrings.
  - Strengthen core musculature (abdomen, hips, and back).
    - — Abdominal muscle strengthening reduces pelvic tilt and decreases the tendency toward lordosis.
    - — Strengthening spinal extensor muscles (eg, by raising the torso and head off the floor/exercise ball while lying prone) is recommended, as decreased strength and endurance of these muscles is associated with lower back pain.
  - May use an exercise ball, yoga, or Pilates instruction.
- Full sit-ups with fixed feet and bent knees should be discouraged.
  - Uses hip flexors rather than abdominal muscles
  - Increases intervertebral disk pressure
- Continuous frequency ultrasonography, massage, and acupuncture may be helpful.
- In leg-length discrepancy, a heel lift and physical therapy to reduce flexion contractures at knee and hip and genu valgus may be of benefit.

Spondylolysis

- Treatment is controversial and may be best managed with a pediatric sports medicine specialist or orthopedic surgeon.
- Provide symptomatic relief.
- Thoracolumbar bracing to prevent extension has been shown to be helpful in some studies; bracing can be used up to 6 months or until the patient is pain free with extension.
- Some experts advocate restricting extension activities without a brace.
- Consider the Williams exercises: physical therapy that promotes abdominal strengthening and hamstring stretching.
- Bone stimulators have been used as adjunctive therapy.

Spondyloarthropathic Conditions

- Anti-inflammatory and immunomodulatory therapies
- Physical therapy

Scheuermann Disease

- Treatment is usually conservative.
  - Physical therapy: strengthening and stretching exercises.
  - Avoid painful activities.
  - Analgesic medication if needed.
- Thoracolumbar bracing and surgery may be indicated if kyphosis exceeds 60°.

WHEN TO REFER

- Prompt and urgent evaluation and referral are needed when back pain is accompanied by
  - Radicular pain down the leg
  - Numbness or tingling
  - Bowel or bladder problems
  - Erectile dysfunction
  - Loss of sphincter tone on rectal examination
  - High clinical suspicion of vertebral osteomyelitis/epidural abscess
- Consider referral for
  - Ankylosing spondylitis and spondyloarthropathic conditions
    - — Refer to pediatric rheumatology.
  - Leukemia, lymphoma, and Ewing sarcoma
    - — Refer to pediatric oncology.
  - Osteoid osteoma
    - — Refer to pediatric orthopedic surgery.
  - Spondylolysis
    - — Refer to a pediatric sports medicine specialist or orthopedic surgery.

- Scheuermann disease
  - Refer to orthopedic surgery (pediatric or spinal) if patients in whom conservative management fails, those with intractable pain, or those in whom kyphosis progresses or when diagnosis and evaluation are outside of scope of expertise.

WHEN TO ADMIT

- Admit patients with back pain with associated fever or neurologic findings or when prompt and thorough diagnostic assessment cannot be completed as an outpatient.

PROGNOSIS

- Prognosis depends on the underlying cause of back pain.

PREVENTION

- Muscular low back pain prevention measures.
- Proper posture.
- Backpack should not exceed 10%–20% of body weight.
- Stretches to improve flexibility of lower back and hamstrings.
- Exercise to strengthen core musculature (abdomen, hips, and back).

Bacterial Skin Infections

DEFINITION

- Bacterial infections of the skin are common and most often caused by gram-positive bacteria.
  - *Staphylococcus aureus*
  - Group A streptococci
- The clinical disease that results depends on the infection's location in the skin.

SIGNS AND SYMPTOMS

Impetigo

- History
  - The patient usually has no history of preceding trauma to the skin.
  - Mild to moderate itching may be associated with lesions.
  - Other family members also may be affected.
- Physical findings
  - Most commonly found on the face.
  - Lesions may be single or multiple and scattered elsewhere on the body as well.
  - Usually yellow- or honey-colored crusts that, when removed, reveal a pink, superficially eroded, glistening base.
    - — A culture sample should be obtained from this base.
  - Intact bullae, if present, contain deceptively clear fluid.
  - Blisters break easily, leaving behind a superficially denuded skin surface covered with a thin, brown, varnish-like crust surrounded by a thin rim of loose, ragged epidermis that represents the remnants of the blister roof.
    - — Surrounding erythema is minimal.
    - — Regional lymphadenopathy is rare.

Pyoderma

- History
  - May occur in epidemics among children of lower socioeconomic status who live in crowded conditions in a warm, humid environment.
  - In contrast to impetigo, lesions occur most commonly on the lower extremities.
  - Usually preceded by trauma such as a scratch or insect bite.
  - Family members may be affected.
- Physical findings
  - Early lesion is a pustule with surrounding erythema.
  - Typically, the more advanced lesion of ecthyma is seen.
  - Lesion appears as a thick, usually brown crust surrounded by erythema.
    - — When the crust is removed, an actual ulcer is revealed.
  - Regional adenopathy is often present.

Folliculitis

- History
  - Appears most commonly as a chronic eruption unaccompanied by symptoms.
  - Occasionally, a patient has mild discomfort or pruritus.
- Physical findings
  - Lesions are usually located on the buttocks and upper portion of the thighs.
  - Scattered individual small papules and pustules.
  - On close inspection, hairs can be seen growing out of the very center of many of the lesions.

Furuncles and Abscesses

- History
  - A history of trauma may be elicited but often is not, especially with furuncles.
  - Immunodeficiency states and diabetes may predispose certain patients to bacterial skin infections.
  - The typical patient with a furuncle or abscess has no underlying medical disease.
- Physical findings
  - Furuncles and abscesses are fluctuant masses filled with pus.
  - Often begin as hard, tender, red nodules that become more fluctuant and painful with time.
  - Abscesses tend to be larger and deeper than furuncles.
  - The 2 lesions may be difficult to differentiate clinically.

Cellulitis

- History
  - Children often feel and appear ill.
  - Fever may precede clinical skin signs.
  - May complain of pain in the affected area; patients who have perianal cellulitis often have pain on defecation.
  - Symptoms of accompanying otitis media may be present in buccal cellulitis.

- Physical findings
  - Fever at the time of presentation is common.
  - The area of involved skin shows the classic signs of inflammation.
    - Redness
    - Swelling
    - Heat
    - Tenderness

DIFFERENTIAL DIAGNOSIS

Impetigo

- Herpes simplex infection is the condition most often confused with impetigo.
- Clinical clues that suggest herpes rather than impetigo include
  - Intact vesicles are more likely in herpes simplex infection.
  - As vesicles age, they become cloudy and ultimately result in crusts that also may be honey colored.
  - The crusted phase most often causes the diagnostic confusion.
- Herpes simplex infection tends to be a recurrent condition.
  - Recurrence is not the case with impetigo.
- When an impetiginous pustule is unroofed, it is noticeably filled with pus.
  - A herpetic lesion may appear to be pus filled, but when it is unroofed, only a scant amount of clear fluid is found.
- In impetigo, Gram staining shows numerous gram-positive cocci.
  - In herpes simplex infection, Wright staining of a scraping from the base of a crust or a vesicle reveals multinucleated giant cells.

Pyoderma

- Ecthyma gangrenosum is an uncommon but serious manifestation of sepsis in immunocompromised hosts.
  - Most frequently associated with *Pseudomonas aeruginosa* infection
  - Can be seen with other gram-negative organisms or even with fungi
- Clinical features that help differentiate this lesion from ecthyma include
  - Location: Ecthyma gangrenosum is often on the upper extremities or in the inguinal or axillary folds.
  - Lesion's appearance: A deeper ulcer is covered with a tightly adherent, black (gangrenous) crust.
  - Host: seriously ill, usually immunocompromised patient with other signs of sepsis.

Folliculitis

- Clinically, folliculitis caused by gram-negative organisms differs from staphylococcal folliculitis in its distribution.
  - Lesions occur primarily on the face and shoulders, often concentrated in the perioral and perirhinal areas.
  - Hot tub folliculitis usually appears on the lower trunk on areas most exposed to the contaminated water in the tub.
- Keratosis pilaris is another common follicular disorder.
  - Exhibits as tiny, rough, scaling papules on back of the upper parts of the arms, buttocks, and thighs.
  - Although its distribution may be similar to that of staphylococcal folliculitis, the appearance of the lesions is not.
    - In keratosis pilaris, the lesions are smaller, more numerous, and scaling but not pustular.

Cellulitis

- Erysipelas
  - A form of cellulitis caused most commonly by group A streptococci.
  - Infection is limited to the upper dermis.
  - Erysipelas has raised and sharply demarcated borders.
  - Bedside differentiation of erysipelas from cellulitis is sometimes difficult.
    - Not particularly useful clinically because therapeutic considerations are the same for both conditions
- Severe, local, confluent contact dermatitis may sometimes be confused with cellulitis.
  - Both may show marked erythema of the skin.
  - Important differences from contact dermatitis include
    - The complaint is of itch rather than pain.
    - The skin usually is not tender.
    - The patient is not febrile.
    - The presence of vesicles also favors contact dermatitis.
    - Vesicles and bullae may sometimes occur in erysipelas or cellulitis as the condition evolves.

Perianal Dermatitis

- Originally thought to be cellulitis but now known to be a more superficial infection.
- May be misdiagnosed as candidiasis or diaper dermatitis.

- Bright-pink erythema and pain or tenderness of the involved skin suggest bacterial infection.
  - A result from a swab culture usually shows *S aureus* or group A streptococci.
  - Laboratory personnel must be aware that they are to look for these organisms; otherwise, they will look for enteric flora with a culture from this site.

Necrotizing Fasciitis

- A fulminant skin infection most often caused by group A streptococci.
  - Flesh-eating bacteria
  - Warm, violaceous, exquisitely tender, and markedly edematous (orange peel–like) skin with indeterminate edges.
  - Systemic toxicity is often seen.
    - Fever
    - Leukocytosis
    - Thrombocytopenia
    - Hypocalcemia
    - Hyponatremia
  - Systemic antibiotics are an adjunct to prompt surgical debridement.

Erythema Infectiosum

- Fifth disease, caused by parvovirus B19
- Erythema of the cheeks, with a slapped-cheek appearance
- Important diagnostic differences between erythema infectiosum and cellulitis
  - Involvement is bilateral.
  - The site is not usually very tender.
  - The patient does not appear toxic.
  - The patient may be mildly febrile.

LABORATORY FINDINGS

- Impetigo
  - Gram stain of the clear blister fluid or serum underlying the crusts shows gram-positive cocci.
  - Cultures grow *S aureus* or *Streptococcus pyogenes*.
- Pyoderma
  - Culture sample taken from the base of the denuded ulcer usually grows group A β-hemolytic *Streptococcus*.
  - *S aureus* is occasionally recovered concomitantly; thought to be a secondary invader.
- Folliculitis
  - Culturing is not usually necessary in the typical case.
  - If presentation is atypical and laboratory confirmation is desired, the contents of a fresh pustule should be cultured.
- Furuncles and abscesses
  - Gram stain of the pustular material may identify the bacterial cause.
  - For precise identification, cultures are required.
    - For anaerobic cultures: Aspirate the pus, seal the syringe, and deliver to the laboratory.
    - If insufficient material is available to aspirate, a swab culture can be used for anaerobic and aerobic cultures.
    - Blood culture results rarely are positive in patients with furuncles or abscesses.
      - Not indicated unless the patient shows signs of sepsis
- Cellulitis
  - Leukocytosis is a common finding.
  - Causative pathogen is usually assumed from history and physical examination.
  - Identification by culture is difficult.
    - Blood culture results are positive in <5% of cases.
  - In neonates or undervaccinated hosts with facial cellulitis, lumbar puncture with culture of cerebrospinal fluid may disclose unsuspected meningitis.

IMAGING

- Ultrasonography
  - Furuncles and abscesses.
    - To avoid unnecessary incision and drainage procedures and ensure appropriate treatment, ultrasound may differentiate between an abscess and cellulitis.
  - An abscess classically has an anechoic or hypoechoic complex fluid collection.
  - Cellulitis usually shows diffuse thickening, increased echogenicity of the skin and subcutaneous tissues, and hypoechoic strands between the fat and connective tissue.

SPECIFIC TREATMENTS

Impetigo

- Topical and systemic antibiotics can be used to treat impetigo.
- Mupirocin topical antibiotic ointment has been reported to equal or exceed the efficacy of oral erythromycin in the treatment of bacterial impetigo and is recommended as initial treatment.
  - Cream form is also available.
  - Topical mupirocin should be considered whenever feasible because it can be effective in treating impetigo caused by methicillin-resistant *S aureus* (MRSA).

- Infected area should be washed carefully and crusts gently removed, if possible, once a day.
- Antibiotic cream or ointment is applied 3 times daily.

- Traditional topical preparations that contain bacitracin or neomycin, either alone or in combination.
  - Poorly absorbed; thus, not particularly effective
- Systemic antibiotics should be used for more extensive lesions.
  - Clindamycin or trimethoprim-sulfamethoxazole might be an appropriate choice in the era of MRSA.
    - However, one study of treatment of skin and soft tissue infections found no benefit over penicillins.
  - Traditional choices in the pre-MRSA era included
    - Erythromycin.
    - Penicillinase-resistant penicillin (eg, dicloxacillin).
    - Amoxicillin-clavulanic acid.
    - Cephalexin.
    - These agents would still be appropriate for treatment of disease caused by methicillin-sensitive *S aureus* or *S pyogenes*.
  - Treatment course should be 7–10 days.
  - Patients with more extensive disease who fail traditional empiric antibiotic therapy should have cultures and susceptibility studies performed.

Pyoderma

- Antibiotics are the treatment of choice, but route of administration is debated.
  - Even in the age of MRSA, penicillin should be first-line therapy.
  - Trimethoprim-sulfamethoxazole monotherapy has higher failure rates than penicillins or clindamycin.
- Prophylactic topical agents, such as mupirocin, may be applied to scratches or insect bites to prevent the development of pyoderma.
- Systemic antibiotics are recommended for streptococcal infections, particularly if the infection is extensive.
  - Injectable benzathine penicillin G.
    - A 7- to 10-day course of oral penicillin or erythromycin is preferred if the patient is likely to be adherent to the prescribed regimen.
  - Penicillin treatment occasionally fails.
    - Most likely because of the persistence of coexisting penicillinase-producing *S aureus* organisms

Folliculitis

- Mild staphylococcal folliculitis can be managed by having the patient use an antiseptic cleanser (eg, chlorhexidine) or antibacterial soap containing triclosan or triclocarban.
  - Use daily or every other day for at least several weeks.
  - Topical clindamycin lotion or solution applied twice daily may be useful.
- For more extensive involvement, a 7- to 10-day course of systemic antibiotics (eg, erythromycin, dicloxacillin) is suggested in addition to the topical regimen.

Furuncles and Abscesses

- Very small furuncles can be treated with moist heat, which promotes drainage.
- For larger furuncles, incision and drainage is the appropriate therapy.
- For furuncles <5 cm in diameter, incision and drainage alone results in complete healing in most cases.
- For abscesses >5 cm or patients with surrounding cellulitis or signs of systemic illness, systemic antibiotics should be used.
- If lesions are seen early in their development, systemic antibiotics may result in involution, obviating the need for incision and drainage.
  - Dicloxacillin, cephalexin, and erythromycin were considered the antibiotics of choice.
  - They need to be reevaluated in light of MRSA in furunculosis.
    - Most community-associated MRSA isolates are susceptible to trimethoprim-sulfamethoxazole.
    - Many are sensitive to clindamycin.
    - Clindamycin has excellent penetration into the infected tissues.
    - Some erythromycin-resistant strains of MRSA have inducible resistance to clindamycin.
  - It is important to know local susceptibility patterns.
- Culture results from abscesses may help in the ultimate selection of the appropriate antibiotic.

Cellulitis

- Systemic antibiotics are the mainstay of therapy.
- Mild cases of cellulitis on an extremity may be treated with
  - Oral antibiotic
  - Warm soaks
  - Outpatient follow-up in several days
- Cellulitis of the extremity most often is caused by gram-positive organisms; thus, the following choices are appropriate:
  - Erythromycin
  - Dicloxacillin
  - Cephalexin
- More seriously ill patients should be hospitalized for parenteral antibiotic therapy.
  - Infants and young children; patients with predisposing medical conditions, such as diabetes mellitus
  - Patients with immunodeficiencies or on immunosuppressive therapies
  - Patients in whom sepsis is suspected
- Community-associated MRSA strains are generally more susceptible to non–β-lactam antibiotics than are nosocomial MRSA strains.
  - Clindamycin
  - Trimethoprim-sulfamethoxazole
- Some erythromycin-resistant strains develop resistance to clindamycin during treatment.
  - The microbiology laboratory should provide results of a D-test for strains resistant to erythromycin.
  - If the D-test result is negative, clindamycin can be used.

WHEN TO ADMIT

- Cellulitis with suspected sepsis or suspected underlying serious infection
- Invasive infections (necrotizing fasciitis)
- Staphylococcal scalded skin syndrome
- Toxic shock syndrome

WHEN TO REFER

- Preseptal cellulitis
- Treatment failure
- Recurrent bacterial skin infections

FOLLOW-UP

- Impetigo
  - Exclusion from school
    - — A child may be asked to leave school until the infection is treated.
    - — The period of infectiousness is unknown.
    - — Most child care centers and schools recommend exclusion as long as open lesions persist.
    - — If lesions are covered, the child can return to school without posing a significant risk to others.

COMPLICATIONS

Impetigo

- If the infection does not respond rapidly to therapy, it may be caused by an antibiotic-resistant strain.
  - In such cases, initial culture and susceptibility results serve as a guide in selecting an alternate antibiotic.
- Historically, differentiating between staphylococcal and streptococcal impetigo was considered to be important.
  - Glomerulonephritis can be a sequela of streptococcal impetigo.
  - Evidence now shows that treatment of streptococcal skin infections does not alter the risk of glomerulonephritis.

Pyoderma

- Cellulitis may develop if the infection extends into larger and deeper areas of skin and subcutaneous tissue.
- Some strains of group A streptococci produce the toxin responsible for scarlet fever.
- Acute glomerulonephritis may follow streptococcal infection of the skin.
  - Caused by only a few nephritogenic serotypes (49, 55, and 57) of pyoderma-inducing streptococci.
  - The usual period from onset of infection to development of glomerulonephritis is 18–21 days.
- Skin infection with streptococci never leads to acute rheumatic fever.

Furuncles and Abscesses

- Recurrent furunculosis
  - Consider an underlying immunodeficiency (rare).
  - Many patients harbor *S aureus* in a sequestered mucocutaneous site, most commonly in the anterior nares.
    - — Apply mupirocin to the external nares twice daily for 5 days.
    - — Repeat the process monthly or every 2 months.
    - — This decreases recurrence by approximately one-half.

- Some recommend an every-other-day total-body scrub with an antiseptic cleansing agent, such as chlorhexidine, or antibacterial soap containing triclosan or triclocarban.
  - — Overuse may dry the skin, harming skin integrity.
- Some advocate the addition of a small amount of bleach to the bathwater to reduce skin colonization.
  - — In a study, a regimen of dilute bleach baths, intranasal mupirocin, and education effectively eradicated *S aureus* over a 4-month period better than topical antibiotics alone or in combination with chlorhexidine.
- Most oral antibiotics do not eradicate nasal carriage of *S aureus,* but clindamycin is an exception.
- In cases that are refractory to all previously described methods, a single oral dose of clindamycin, given daily for 3 months, may be effective at eliminating recurrences.

- In rare cases, a staphylococcal abscess may be the focus of toxin production.
  - Can result in
    - — Staphylococcal scalded skin syndrome, most commonly seen in infants and neonates
    - — Toxic shock syndrome
    - — Staphylococcal scarlet fever

Cellulitis

- In some instances, findings that are clinically diagnosed as cellulitis may actually be a clue to underlying, deeper-seated infection.
  - Cellulitis of the periorbital tissues may be secondary to sinusitis.
  - Abdominal wall cellulitis may hide an underlying peritonitis.
  - Redness, warmth, and swelling of tissues overlying bones or joints may indicate septic arthritis or osteomyelitis.
  - Facial cellulitis may be caused by an undiagnosed dental abscess.
  - Redness of the neck is sometimes a clue to underlying deep neck space infections.
  - Inflammation of the skin of the sacrum might be from an infected pilonidal cyst.
  - Redness of the pinna or postauricular area may point to malignant otitis externa or mastoiditis.
- Uncomplicated cellulitis was once a serious, life-threatening disease, but antibiotics have now reduced the fatality rate to nearly zero in otherwise healthy patients.

PROGNOSIS

- Impetigo
  - With appropriate antibiotic therapy, prompt healing is expected.
  - Bacteriologic cures occur within 7–10 days.
- Pyoderma
  - In most patients, the lesions heal uneventfully.
  - Because they are deeper, streptococcal lesions often take longer than staphylococcal lesions to heal.
  - Bacteriologic cures are usually accomplished within 1 week.
    - — If prompt response is not achieved, secondary infection from a penicillinase-producing staphylococcal strain should be considered, particularly if penicillin was used for treatment.
    - — Erythromycin-resistant strains of group A streptococci may be encountered.
- Folliculitis
  - Most patients respond to treatment.
  - If not, bacterial culture should be performed to rule out infection by gram-negative organisms or MRSA.
  - Some patients are plagued with recurrences, for which a more prolonged course of antibiotic therapy is recommended.
  - In rare cases, the follicular infection extends deeply, producing a furuncle.
- Furuncles and abscesses
  - Untreated lesions often rupture and drain spontaneously.
  - After surgical or spontaneous drainage, uneventful healing is the rule.
  - Larger lesions may leave scars.
- Cellulitis
  - With appropriate antibiotic therapy, fever usually resolves within 24 hours.
  - If it does not, a change in antibiotic therapy should be considered, optimally guided by early culture and bacterial sensitivity results.
  - The skin reaction resolves more slowly than does fever, sometimes taking ≥1 weeks to subside completely.

Bronchiolitis

DEFINITION

- Bronchiolitis is a common, acute viral lower respiratory tract illness of newborns, infants, and children, occurring during the first 2 years of life.
- In bronchiolitis, acute inflammation of the airways results in
  - Wheezing
  - Hyperinflation
  - Tachypnea

SIGNS AND SYMPTOMS

- Fluctuation of physical findings on examination is characteristic.
- Acute onset of wheezing.
  - Auscultation usually reveals wheezing with or without crackles, but findings may vary from hour to hour.
  - Decrease in the auscultatory findings accompanied by increasing respiratory distress may indicate progressive obstruction to the flow of air in the small airways and impending respiratory failure.
- Increased respiratory rate is almost always evident.
  - Tachypnea must be judged on the basis of age.
    - Reference respiratory rate
      - 50 breaths per minute in full-term newborns
      - 40 breaths per minute at 6 months of age
      - 30 breaths per minute at 1 year of age
  - Tachycardia commonly accompanies tachypnea.
- Acute inflammation of the airways.
- Infants with bronchiolitis typically have a recent history of signs compatible with a common cold.
  - Rhinorrhea
  - Nasal congestion
  - A low-grade fever
  - Cough
    - More common as infection spreads to the lower respiratory tract
    - Followed by tachypnea
  - Fever (in ~50% of infants at diagnosis)
- Clinical appearance.
  - Infant may appear irritable, lethargic, or anxious.
  - Signs of increased work of breathing and airway obstruction.
  - Flaring of the nasal alae and expiratory grunting.
  - Retractions of the chest wall in the subcostal, intercostal, and suprasternal areas.
  - Use of the accessory muscles of respiration.
  - Prolonged expiration that may be difficult to detect in a neonate and young infant who has a rapid respiratory rate.
  - Impeded flow of air on inspiration (to a lesser extent).
  - Hyperinflation.
    - Increased diameter of the chest
    - Hyperresonance on percussion
  - Liver and spleen may become easily palpable from the downward placement of over-inflated lungs.
- Clinical findings may develop from acute complications during the infant's course.
  - Apnea
    - Infrequent but potentially fatal
    - Risk of apnea greatest in
      - Infants of preterm gestation
      - Postmenstrual age at the time of presentation <44 weeks
  - Otitis media
    - Present in 3%–30% of infants
    - May be caused by the infecting virus, bacteria, or both
  - Dehydration from
    - Paroxysms of coughing that trigger vomiting
    - Decreased fluid intake resulting from congested nasal passages
    - Respiratory distress
    - Tachypnea
    - Fever
  - Aspiration
    - Seen frequently in infants hospitalized with respiratory syncytial virus (RSV) bronchiolitis
    - Correlated with an increased risk of subsequent hyperactive airway disease
    - Abrogated by the prophylactic administration of thickened feeds

DIFFERENTIAL DIAGNOSIS

- Asthma
  - Wheezing and respiratory distress are associated with bronchiolitis and asthma in young children.
  - In a single episode, differentiating these 2 entities is often not possible.
  - Both asthma and bronchiolitis may be engendered by viral infection.
    - Differentiation is confounded by the possibility of a link between them.
    - RSV infection in infancy may lead to subsequent wheezing associated with asthma.
  - Previous wheezing episodes and family history of atopy are more suggestive of asthma.

- Gastroesophageal reflux
  - The infant may exhibit episodes of wheezing clinically identical to bronchiolitis.
  - History of the timing of feeding and frequency of wheezing, and lack of upper respiratory tract signs typical of a viral infection, are helpful in differentiating.
- Other entities that may result in wheezing and respiratory distress in the bronchiolitic age group include
  - Obstruction from an aspirated foreign body
  - A vascular ring
  - Retropharyngeal abscess
  - Significantly enlarged adenoid (rarely)
- Wheezing may also occur in
  - Congestive heart failure
  - Chronic lung disease (eg, with preterm birth or cystic fibrosis)

DIAGNOSTIC APPROACH

- Diagnosis of bronchiolitis is usually based on clinical history and physical findings.
  - Features that strongly support the diagnosis include
    - Illness occurring during a community outbreak of a major viral agent, mainly RSV
    - Young age (especially <12 months)
    - No prior episode of wheezing
  - Assess risk factors for the development of more severe disease, especially
    - Presence of preterm birth
    - Cardiopulmonary disease
    - Immunodeficiency
    - Other underlying diseases
  - Recent history of signs compatible with a common cold
  - Fever
    - Commonly present during the prodromal period and usually not high.
    - By the time infants or children exhibit bronchiolitis associated with RSV, only ~50% are febrile.

LABORATORY FINDINGS

- Laboratory diagnostic tests
  - Not routinely recommended for typical infants at first episode of wheezing.
  - Except in atypical cases or with abrupt clinical changes, such tests as complete blood cell count, arterial oxygen saturation, serum chemistries, and cultures to rule out bacterial infection are generally not helpful or necessary.
- Pulse oximetry
  - Not shown to improve outcomes for infants with bronchiolitis
  - Use in hospitalized patients has been associated with
    - Lower threshold for hospitalization
    - Higher rates of admission to intensive care units and mechanical ventilation
- Viral identification
  - Not routinely recommended.
  - Assays to identify the specific virus may be warranted
    - In more severely ill infants and children in whom specific antiviral therapy for RSV or influenza is considered
    - In determining feasible infection control procedures, such as in a cohort
  - Laboratory assays most commonly used to determine the viral causes are rapid antigen detection assays.
- Rapid viral diagnostic techniques
  - Have variable sensitivities.
  - Should be used only when the virus is prevalent in the community, preferably during peak period of activity.
    - Positive predictive value is low when little circulation of the virus occurs in the area.
    - False-positive rate increases as the incidence of the disease in the community falls.
  - Detect within hours some types of viruses in respiratory secretions that commonly cause bronchiolitis.
  - Rapid antigen detection kits are available for most viruses implicated in bronchiolitis, including RSV, parainfluenza viruses, influenza viruses, and hMPV.
  - Reverse transcriptase polymerase chain reaction (RT-PCR) and other molecular diagnostic assays are highly sensitive and specific for multiple viral agents.
    - Confusion may result from their ability to detect infecting agents over prolonged periods.
  - Quantitative PCR assays may help in some instances.
  - Viral isolation techniques are rarely used and RT-PCR has been demonstrated to be significantly more sensitive.
- Antibody determinations on acute and convalescent sera in neonates and young infants are rarely helpful because of
  - Time required to obtain a convalescent serum
  - Presence of passive maternal antibody

- Diminished antibody response of neonates and young infants to some viral respiratory agents causing bronchiolitis

IMAGING

- Imaging may be helpful when
  - Diagnosis is not clear.
  - Course is not as expected.
- It should not be used routinely when
  - The child was previously typical.
  - Diagnosis can be made based on clinical and historical findings.
  - Monitoring the course of an infant with bronchiolitis.
  - Making admission or discharge decisions.
- Findings on chest radiography
  - Are commonly relatively benign.
  - Do not correlate with severity of illness.
- Classical findings
  - Increased bronchovascular markings radiating out from the hila
  - Scattered small areas of atelectasis
    - May be mistakenly interpreted as pneumonic infiltration and bacterial infection
- In prospective studies of children with suspected lower respiratory tract infection, those evaluated with chest radiography
  - Were more likely to receive antibiotics
  - Did not have improved outcome or reduced duration of illness

TREATMENT APPROACH

- Little agreement exists as to the value and use of therapeutic modalities.
- Management consists primarily of
  - Supportive care, including adequate rest
  - Comfort
  - Hydration
  - Antipyretics, if necessary

SPECIFIC TREATMENTS

Congestion of Nasal Passages and Upper Airway

- May be alleviated by gentle nasal suctioning and positioning.
- Mist therapy has not been shown to be beneficial.

Supplemental Oxygen

- For the severely affected newborn, infant, or child who is hospitalized
  - Supplemental oxygen, as indicated by repetitive readings indicating inadequate oxygen saturation
  - No consensus as to the level of oxygen saturation that indicates the need for supplemental oxygen
- Recent bronchiolitis guidelines from the American Academy of Pediatrics (AAP) recommend
  - Initiating supplemental oxygen when the oxyhemoglobin saturation is persistently <90%
  - Considering discontinuing supplemental oxygen when the level is persistently ≥90%

Common Therapies

- Frequently used, especially in those wheezing for the first time, although evidence showing benefit is lacking.
  - Corticosteroids
  - Antivirals
  - Antibiotics
- Bronchodilators.
  - Studies evaluating their use in bronchiolitis have given variable and contrasting results.
  - Most controlled trials and reviews of β-adrenergic agents have shown
    - No consistent clinical benefit in children hospitalized with their first episode of wheezing
    - Transient or short-term clinical benefit in outpatients when evaluated by varying clinical score systems
  - The AAP recommends that bronchodilators not be used routinely in the management of bronchiolitis, but a carefully monitored trial of inhaled α- or β-adrenergic agents is an option.
    - Bronchodilators should be continued only if a beneficial clinical response is clearly documented.
- Corticosteroids.
  - In some facilities, most infants with bronchiolitis are treated with systemic glucocorticosteroids.
  - Meta-analyses have not shown consistent or statistically significant benefit in clinical scores, rates of hospitalization, or outcome.
  - The largest multicenter double-blind randomized trial was conducted in 20 emergency departments and completed in 2006.
    - Infants 2–12 months of age with a first episode of wheezing from moderate to severe bronchiolitis received a single dose of one of the following medications over 3 respiratory seasons:
      - Oral dexamethasone (1 mg/kg) *or*
      - Placebo

  - No significant difference was observed in the requirement for hospitalization.
  - The same lack of benefit was observed in subgroups of infants with asthma or with family history of asthma.
- The AAP recommends that corticosteroid medications not be used routinely for care of infants with a first episode of bronchiolitis.

- Antivirals.
  - Few antivirals are potentially useful against the viral agents that cause bronchiolitis.
  - Inhaled ribavirin (a synthetic nucleoside)
    - Only agent currently approved for the treatment of RSV lower respiratory tract disease in infants.
    - Not recommended routinely to treat infants and children with bronchiolitis.
    - Generally should only be considered for use in infants at high risk for severe disease.
    - Expensive; difficult to administer to ventilated patients.
    - Benefits in clinical outcome are controversial.
    - Use should be decided on an individual basis after consideration of relative benefit to cost.
    - Antivirals for influenza have not been approved for neonates <14 days of age or evaluated in bronchiolitis management.
- Antibiotics.
  - Should not be used unless
    - Bacterial infection is documented *or*
    - Evidence strongly indicates concurrent presence of a bacterial infection.
  - Bacterial infection is uncommon in bronchiolitis and RSV lower respiratory tract disease.
- Chest physiotherapy, including percussion and vibratory techniques.
  - Have shown no clinical value
  - Are not recommended

WHEN TO ADMIT

- Oral intake is inadequate.
- Newborn, infant, or child appears toxic or has marked tachypnea or lethargy.
- Respiratory distress is rapidly progressive.
- History suggests apneic episodes.

WHEN TO REFER

- Episodes of bronchiolitis or wheezing are recurrent or started at birth.
- Wheezing continues despite clinical improvement.

COMPLICATIONS

- Apnea
  - Initial manifestation of illness in 10%–20% of newborns and infants
  - Most at risk of apnea
    - Newborns and infants of preterm gestation
    - Newborns and infants whose postmenstrual age is <44 weeks
  - Subsequent prognosis for infants and children with apnea associated with RSV infection is generally good.
  - Does not appear to be associated with increased risk of subsequent apnea, even during subsequent viral infections.
- Otitis media
  - Present in 3%–30% of infants
  - May be caused by infecting virus, bacteria, or both
- Risk of dehydration from
  - Paroxysms of coughing that trigger vomiting
  - Decreased fluid intake resulting from congested nasal passages
  - Respiratory distress
  - Tachypnea
  - Fever
- Aspiration
  - Frequent among infants hospitalized with RSV bronchiolitis
  - Correlated with increased risk of subsequent hyperactive airway disease
  - Shown to be abrogated by (prophylactic) administration of thickened feeds

PROGNOSIS

- Most infants improve appreciably within several days.
- Cough and other respiratory signs resolve gradually over 1–2 weeks.
- Most hospitalized infants and children are discharged within days, often 2–3.
- Radiographic resolution of atelectasis may require several weeks.
- In ambulatory infants and children
  - Median duration has been reported to be 12 days for infants and children <24 months.
  - 18% are symptomatic after 3 weeks.
  - 9% are symptomatic after 4 weeks.
- Clinical course tends to be more prolonged in
  - Neonates and young infants
  - Those with underlying conditions
  - Those who acquired the infection nosocomially

- Some studies suggest increase in severity of infection when >1 virus is present; others do not.
- Despite the increase in hospitalizations, mortality associated with bronchiolitis and RSV has declined.
- Recurrent wheezing.
  - The most frequent sequelae of bronchiolitis, especially that caused by RSV.
  - Reported in 30%–50% of the infants and children hospitalized for bronchiolitis.
  - Episodes tend to occur most frequently during the first 2 years after the initial bronchiolitis.
  - Most of these infants and children subsequently improve and become asymptomatic.
- Lung function abnormalities may persist beyond 10 years, despite clinical improvement.
  - Significantly reduced mean expiratory flow rates and increased risk of bronchial hyperreactivity during adolescence have been demonstrated.
  - One episode of bronchiolitis and less severe bronchiolitis not requiring hospitalization have not been associated with later pulmonary abnormalities.
- Relationship between bronchiolitis in early infancy and subsequent hyperreactive airway disease is unclear and confounded by the increasing recognition that asthma or reactive airway disease is a heterogeneous group of disorders with variable pathogenesis.
  - Some follow-up studies have shown that, by school age, risk of hyperreactive airway disease is not greater than in children with no history of bronchiolitis.
- Prognosis for children with apnea associated with RSV infection is generally good.
  - Does not appear to be associated with increased risk of apnea later, even during subsequent viral infections.

Bulimia Nervosa

DEFINITION

- Eating disorder involving recurrent episodes of binge eating, along with purging behaviors
- In *Diagnostic and Statistical Manual of Mental Disorders*, 5th Edition (*DSM-5*)
  - Bingeing requirement has been reduced from twice to once per week.
  - A category for purging disorder has been added.

SIGNS AND SYMPTOMS

- Recurrent episodes of binge eating, characterized by both
  - Eating, in a discrete period (eg, within any 2-hour period), more than most people would eat during a similar period, under similar circumstances
  - Sense of lack of control over eating during the episode (ie, the person feels that she or he cannot stop eating or control what/how much she or he is eating)
- Compensatory behavior to prevent weight gain (at least once a week for 3 months).
  - Self-induced vomiting
    - Examine hands for the Russell sign (ie, irritation on the dorsum of the joints of fingers used to induce vomiting).
    - Erosion of tooth enamel as a result of vomiting.
    - Parotid enlargement.
  - Misuse of laxatives, diuretics, enemas, or other medications
  - Fasting
  - Excessive exercise
- Symptoms of malnutrition.
  - Cold hands and feet
  - Hair loss
  - Irregular menses
- Symptoms related to purging.
  - Heartburn
  - Hematemesis
  - Constipation
  - Diarrhea
- Vital signs: Begin initial physical examination with measurements of weight, height, blood pressure, and pulse.
  - Indicators of diet pill use
    - Tachycardia
    - Hypertension
  - Indicators of stimulant laxative or diuretic use
    - Tachycardia
    - Hypotension
  - Excessive exercise may result in significant bradycardia with resting heart.
  - If dehydration needs to be ruled out, measure blood pressure for orthostatic changes (see Diagnostic Procedures section).

DIFFERENTIAL DIAGNOSIS

- Other medical causes of weight loss or vomiting
  - Cancer
  - Central nervous system tumors
  - Gastrointestinal problems
    - Malabsorption
    - Celiac disease
    - Inflammatory bowel disease
  - Endocrinologic problems
    - Diabetes mellitus
    - Hyperthyroidism
    - Hypopituitarism
  - Chronic illnesses and chronic infections
  - Superior mesenteric artery syndrome
- Psychiatric causes of weight loss
  - Depression
  - Obsessive-compulsive disorder
  - Psychosis (especially schizophrenia)
  - Sleep disorders
  - Hallucinations, delusions, or obsessions

DIAGNOSTIC APPROACH

- History should include
  - Frequency of bingeing and purging
  - Maximum, minimum, and usual weight
  - Patient's eating and exercise patterns
  - Vomiting habits
- Evaluate any medications designed to promote weight loss.
  - Diet pills
  - Laxatives
  - Diuretics
  - Ipecac
- Avoid being misled by the patient; physical examination and laboratory tests suggest the true extent of the disorder.
- The patient may be underweight, overweight, or typical weight.
- Specific abnormalities on physical examination are rarely found; subtle changes in vital signs, physical examination, and laboratory tests should be sought.
- Full psychosocial history must be obtained to establish diagnosis and the psychosocial severity of the disorder.
  - Patient's functioning in the family, in school, and among peers

- Possible psychiatric symptoms
  - — Sleep disorders
  - — Hallucinations, delusions, or obsessions
- Psychosocial changes
  - Fighting with family.
  - Withdrawing from friends.
  - Performing less optimally in school, or improved school performance as withdrawal from friends and family intensifies.
  - If additional psychiatric symptoms are found, the possibility of an additional diagnosis should be pursued.

LABORATORY FINDINGS

- Blood tests
  - Complete blood cell count with differential
  - Electrolytes and serum chemistry
  - Lipid studies
  - Liver function tests
  - Amylase (Levels are elevated.)
- Urine tests
  - Urinary pH may be elevated.
  - Urinalysis may reveal
    - — Elevated specific gravity in dehydration
    - — Elevated ketones in starvation
    - — Increased pH in presence of vomiting
- Hormone tests, if menstrual periods are problematic
  - Thyroid function tests
  - Luteinizing hormone
  - Follicle-stimulating hormone
  - Estradiol
  - Prolactin (if amenorrheic)
- Echocardiography
  - If potassium levels are abnormal
  - If history of ipecac use
- Bone density test for osteopenia
  - If oligomenorrheic or amenorrheic

IMAGING

- Magnetic resonance imaging of the brain, gastrointestinal series, or other tests may be considered for patients who claim to be eating well or not vomiting on purpose.

DIAGNOSTIC PROCEDURES

- To document orthostatic changes
  - Check blood pressure and pulse with patient in the sitting position, followed by standing for 2 minutes.
  - Significant changes
    - — Increase of 20 beats per minute in pulse
    - — Decrease of 20 mm Hg in systolic blood pressure
    - — Decrease of 10 mm Hg in diastolic blood pressure

TREATMENT APPROACH

- Medical and nutritional rehabilitation are crucial.
  - Restoration of body weight to within 10% of ideal body weight (IBW), with restoration of menses, are primary goals.
  - If malnutrition is mild to moderate (15%–25% below IBW), restoration may be accomplished on outpatient basis.
  - If malnutrition is moderate to severe (>25% below IBW), treatment usually requires hospitalization.
- Medical treatment includes management of
  - Electrolyte abnormalities.
  - Cardiovascular issues.
  - Endocrine disorders.
  - Other organ system dysfunction.
  - These are managed simultaneously with or aided by nutritional rehabilitation.
- Nutritional therapy.
  - Daily intake of 3 substantial meals and 3–4 snacks is usually sufficient for required weight gain.
  - At inpatient units, meals are generally provided as part of a strict regimen, and snacks generally consist of high-calorie supplements.
  - Too-rapid weight gain is associated with severe metabolic abnormalities in some patients (refeeding syndrome).
  - Slow refeeding and phosphorus supplementation are required in patients with severe malnutrition to prevent refeeding syndrome (which can involve cardiac failure, hemolysis, coma, and death).
  - Medical rehabilitation is focused on treating physical symptoms or laboratory abnormalities and stopping or at least decreasing participation in risky behaviors (eg, bingeing, vomiting, laxative and diet pill abuse).
  - Nutritional rehabilitation is focused on normalizing eating patterns and ensuring balanced nutrition.

- A team approach is most often used, consisting of
  - Primary care physician.
  - Psychiatrist.
  - Psychologist or social worker.
  - Nutritionist.
  - The exact combination should be determined by local expertise, availability, and preference.
  - Team meetings/discussions should be held frequently to prevent miscommunication that can sabotage treatment.
- If hospitalization is necessary for uncontrolled binge or purge cycles, abnormal electrolytes, or unstable vital signs, supervision after meals, locked bathrooms, and restricted access to food are often needed.
- Treatment settings.
  - Inpatient and residential settings
    - Patients are admitted to inpatient hospitals for medically or psychiatrically emergent reasons.
    - Protocols to ensure weight gain and to guard against refeeding syndrome.
    - Many begin with food, move to oral supplements or nasogastric feeds if meals are not consistently consumed.
    - Some evidence suggests that using nasogastric tubes at the time of admission can increase rate of weight gain.
    - After stabilization, patients are often transferred to residential programs with less medical monitoring and more psychological support.
    - Behavioral approaches.
      - Include several phases of treatment, with patients moving to another phase based on progressively higher weight goals or improved behaviors or attitudes.
      - Each phase incorporates privileges added to daily activities (eg, food choices, food preparation, passes for outings with program, passes with family).
  - Day programs and intensive outpatient programs
    - Day program
      - Patients ready to leave the residential setting are stepped down to a day program.
      - Generally runs 5 days/wk, providing 2–3 meals and snacks/d.
    - Intensive outpatient program
      - Step down to an intensive outpatient program.
      - Generally runs 3 h/d, 3 d/wk, providing a meal and a group.
    - In both settings, patients still live at home, and with intensive outpatient programs, patients can attend school.
    - Often, intensive outpatient programs and day programs are used as a step up from a general outpatient setting to avoid the next higher level of care.
  - Outpatient settings
    - Least intensive option often includes
      - Medical monitoring
      - Nutritional support
      - Psychiatric support therapy (individual, family, and/or group therapy)

SPECIFIC TREATMENTS

Therapy Options

- Most common
  - Individual therapy
    - Varied
    - Difficult to study
  - Cognitive behavioral therapy (CBT)
    - Decreasing nutritional restriction
    - Normalizing eating
    - Changing perceptions and over concern with body weight and shape
  - Dialectical behavioral therapy
  - Family-based treatment (FBT)
    - Often called the *Maudsley approach.*
    - No blame placed on parents or patient.
    - Parents need to manage the patient's eating because the patient has not and has jeopardized her or his health.
    - Parents are empowered to refeed their child.
    - The entire family is involved in treatment.
    - 3 phases are
      - Refeeding by caregivers
      - Transferring eating responsibility back to the patient
      - Relapse prevention
    - Therapist needs to be trained in this method.
    - Using this method, 50%–60% of patients are in remission by the end of the first year, 25%–35% practically recover, and 15% are resistant.
    - In comparison, <50% of patients who receive more traditional treatment recover within 2–5 years, one-third partially recover, and 20% are resistant.
    - FBT has become a first-line treatment when a trained therapist is available.

B

Dietary Plan

- An appropriate meal pattern may be developed on the basis of the patient's and family's prior eating habits or a specific dietary plan offered by the physician, nutritionist, or, if they are in FBT, the parents.
- The plan should be specific to prevent ambiguities that can lead to family fighting.
- The plan should provide 2,000–3,000 calories daily.
  - Some may be supplied as high-calorie supplements.
  - A similar plan without high-calorie supplements may be offered to healthy-weight patients with bulimia who require nutritional adjustment rather than rehabilitation.
  - Caloric requirements depend on need for weight gain, loss, or maintenance.
- Because caloric restriction may spark binge eating, a nonrestrictive, well-balanced diet should be implemented.
- The diet should be balanced and include foods from each major food group.
- Outpatient gains should be 1–2 lb (0.45–0.91 kg) per week.
- Inpatient gains may be 2–4 lb (0.91–1.81 kg) per week.
- Compliance may be evaluated with a diet diary, but many patients do not keep records accurately and honestly.

Psychopharmacologic Treatments

- Selective serotonin reuptake inhibitor (SSRI) antidepressants.
  - Can treat concurrent psychiatric disorder.
  - May diminish urge to binge and purge and help treat obsessive-compulsive symptoms.
  - Only physicians familiar with their use should prescribe SSRIs, given concerns about associated increased risk of suicide in a minority of children and adolescents.
  - Not effective in treating symptoms of depression or obsessive-compulsive disorder when body weight is low.
- Atypical antipsychotic agents at low doses can improve weight gain and treat symptoms of depression and obsessional thoughts.
  - Other antidepressant medications, roughly equivalent to SSRIs
    - Tricyclics
    - Monoamine oxidase inhibitors
    - Fluoxetine at 60 mg per day
      - Decreases bulimic symptoms
      - Relieves symptoms of depression and anxiety
      - Decreasing concerns with shape, weight, and desire to restrict food intake
      - Anticonvulsants studied with modest changes in symptoms
      - Serotonergic agents and lithium studied with no significant changes in symptoms
  - Tricyclics, monoamine oxidase inhibitors, and SSRIs seem to be roughly equivalent in decreasing bulimic behaviors at the end of short-term treatment.
  - With any of these medications, ~30% of patients are abstinent and 70% have decreased bulimic behaviors.
- Use of CBT, followed by the introduction of medication, if necessary, has been suggested as a logical treatment approach.
- Menses restoration in those with amenorrhea.
  - Generally requires an estradiol level >30 mg/dL.
  - Estrogen replacement has not been shown to reverse or prevent bone loss.
  - Oral estrogen-progesterone combinations pills are not effective in increasing bone density.
  - Physiologic estrogen replacement in the form of a transdermal patch along with cyclic progesterone increases rate of bone accrual in adolescents with anorexia nervosa to the level of age-matched controls.
  - Regaining weight is the only definitive treatment to bring about the return of menses.

WHEN TO ADMIT

- Syncope
- Serum potassium concentration, 3.2 mmol/L
- Serum chloride concentration <88 mmol/L
- Esophageal tears
- Cardiac arrhythmias, including prolonged QTc
- Hypothermia
- Suicide risk
- Intractable vomiting
- Hematemesis
- Failure to respond to outpatient treatment

WHEN TO REFER

- If the patient is medically stable, refer to a therapist skilled in FBT, if available.
- If not, refer to a dietitian to reinforce physician's nutritional recommendations or to set a nutritional plan with the patient.

- Refer to a psychotherapist if
  - Patient is open to therapy.
  - Patient cannot attain goals set by the physician, even if the patient is resistant to psychotherapy.
- Refer for psychopharmacologic evaluation if
  - The patient is bingeing and open to medication.
  - Obsessive-compulsive symptoms are interfering with treatment.
- Refer to adolescent medicine specialist if
  - The primary care physician is not comfortable treating the patient.
  - The primary care physician does not have the time to treat.
  - The patient does not adhere to the physician's treatment plan.

COMPLICATIONS

- Hypertension or hypotension
- Electrolyte abnormalities
  - Hypokalemia
  - Hypochloremia
  - Elevated serum bicarbonate
- Dehydration
- Erosion of dental enamel
- Calluses on the dorsum of the hand
- Parotid enlargement
- Acute pancreatitis
- Acute gastric dilatation or rupture
- Mallory-Weiss tears
- Gastric and esophageal irritation
- Gastric and esophageal bleeding
- Gastroesophageal reflux disease
- Barrett syndrome
- Aspiration pneumonia
- Diarrhea, constipation, steatorrhea
- Emetine cardiomyopathy
- Menstrual irregularity
- Polycystic ovarian syndrome
- Osteopenia, osteoporosis

PROGNOSIS

- ~70% of patients recover.
- 20%–30% experience relapse.
- 10% continue to meet full criteria for bulimia nervosa 5 years after diagnosis.
- Mortality is greater for those with anorexia nervosa compared with bulimia nervosa.

PREVENTION

- Increasing evidence that eating disorder and obesity may be related, with dieting, weight-related teasing, and body dissatisfaction as risk factors; therefore, an integrated approach to prevention is sensible.
- Programs geared toward teenaged boys and girls, primarily in school settings.
  - Maintaining healthy body image, healthy eating.
  - Promoting self-esteem without relation to weight.
  - Increasing awareness and knowledge about eating disorders.
  - Effectiveness is debatable.
- Programs focused on building self-esteem/ comprehensive school-based approach.
  - Classroom interventions
  - Staff training throughout the school
  - Informal discussions between staff and students
  - Integration of material about eating issues into the curriculum
  - More intensive work with persons at high risk
  - Changes in the school with respect to cafeteria food and physical education
  - Referrals and outreach within the school and to the community
- Early case detection and treatment are the most effective preventive measures.
  - Treatment will be easier.
  - Disease will be less entrenched.
  - Families, friends, school personnel, and health professionals must be vigilant for signs of an eating disorder so that early treatment can be initiated.

Cardiac Arrhythmias

DEFINITION

- Cardiac arrhythmias comprise a spectrum of variations to normal heartbeat.
- Normal rhythm variations
  - A wide range of normal heart rates is present in young persons.
- Premature (early) beats
  - Usually benign arrhythmias that occur as
    - Atrial premature contractions (APCs)
    - Premature ventricular contractions (PVCs)
  - Couplet
    - 2 premature beats in a row
  - Bigeminal or trigeminal rhythm
    - Every second or third beat is a premature impulse.
- Supraventricular tachycardia (SVT)
  - Tachycardia with origin above the ventricles
- Atrial flutter
  - Primary atrial reentrant tachycardia
  - Intra-atrial reentrant tachycardia (IART)
- Atrial fibrillation
  - Irregular tachycardia with variable atrioventricular (AV) conduction
  - Types
    - Idiopathic
    - Underlying heart disease
- Ventricular tachycardia (VT)
  - ≥3 repetitive excitations arising from the ventricles, with a rate >120 beats per minute (bpm) or 25% faster than the sinus rate
- Conduction abnormalities
  - First-degree AV block
  - Mobitz type I second-degree AV block
    - Wenckebach block
  - Mobitz type II second-degree AV block
  - Complete AV block (CAVB)
- Sudden cardiac death

HISTORY

- Thorough family history focuses on
  - Sudden death
  - Premature death
  - Syncope
  - Seizures
  - Recurrent arrhythmias
- Typical symptoms include
  - Palpitations
  - Light-headedness
  - Syncope
  - Visceral chest pain
  - Dyspnea
- Nonspecific signs and symptoms of arrhythmia
  - Infants
    - Fatigue
    - Malaise
    - Poor feeding
    - Nausea
    - Pallor
- Premature beats
  - Most have no obvious incitant.
  - Observed most often in healthy children and adolescents.
  - Associated with
    - Myocarditis
    - Hypertrophic cardiomyopathy
    - Dilated cardiomyopathy
    - Ventricular dysfunction
    - Congenital cardiac malformations
    - Sympathomimetics
    - Stimulant drugs
    - Electrolyte imbalances
    - Intracardiac catheters
- SVT
  - Onset
    - First 4 months of life (~50%)
    - >5 years: associated with high probability of recurrence
  - Wolff-Parkinson-White (WPW) syndrome
    - May be inherited in an autosomal-dominant fashion
- Risk factors for atrial flutter
  - Cardiomyopathy
  - Previous repair of complex congenital heart malformation lesions (Fontan procedure)
- Risk factors for atrial fibrillation
  - Structural heart disease
  - Cardiomyopathies
  - Alcohol binges
- Risk factors for VT
  - Myocarditis
  - Repaired and unrepaired congenital cardiac lesions
  - Cardiomyopathies
  - Long QT syndrome (LQTS), short QT syndrome
  - Catecholamine use
  - Exercise-induced VT
  - Marked electrolyte imbalances
  - Use of street drugs (eg, cocaine)
  - Ventricular tumors, especially if drug resistant and incessant
  - Mitochondrial fatty acid beta-oxidation disorders in neonates

- Conduction abnormalities
  - Risk factors in acquired conduction abnormalities
    - Conduction system injury during repair of congenital cardiac malformations
    - Myocarditis
    - Lyme disease
  - Risk factors in CCAVB
    - Complex structural heart disease (~50% of affected patients)
    - Levo-transposition of the great vessels
    - Complex AV septal defects
    - Immune-mediated block in utero from mother with overt or occult autoimmune disease (~50% of affected patients)
      - <5% of newborns born to mothers who have autoimmune disease develop CCAVB.
      - If a mother bears 1 child who has CCAVB, the risk in future pregnancies is 15%.
  - Prolonged QT interval (up to 25%)
  - Fetal hydrops
  - Preterm birth
  - Congestive heart failure
  - Ventricular ectopy
  - AV valve insufficiency
  - Low or decreasing ventricular rate (≤55 bpm in a neonate)
- Risk factors in sudden cardiac death
  - Repaired complex congenital heart malformations
  - Cardiomyopathies
  - Myocarditis
  - Drugs that prolong QT interval
    - Cisapride
    - Imipramine
    - Pentamidine
  - Congenital coronary artery anomalies
    - Especially origin of the left main coronary artery from the right sinus of Valsalva (sinus aortae)
  - Acquired coronary artery anomalies
- Kawasaki disease
- Primary arrhythmias
  - LQTS
  - WPW syndrome
  - Catecholamine-sensitive polymorphic VT
- Associated conditions
  - Congenital deafness (Romano-Ward syndrome)

PHYSICAL EXAMINATION

Normal Rhythm Variations in Childhood

- Sinus arrhythmia (phasic respiratory variations of sinus rate with inspiratory acceleration and expiratory slowing)
- Fast heart rates
  - Sinus tachycardia at rates of 230–250 bpm during infancy have been documented.
  - A rate >200 bpm in a teenager who is not involved in maximal exertion would be abnormal.
- Slow heart rates/sinus bradycardia
  - Sinus rate below that expected for a patient's age.
  - Greater reason for alarm than fast rates.
  - Sinus rate <100 bpm in an awake neonate is abnormal.
  - During sleep, rates down to 80 bpm are common.
  - Brief dips into the 60–80 bpm range are also observed in sleeping neonates during normal, vagally induced episodes of junctional rhythm.
  - A highly conditioned adolescent endurance athlete may have a resting heart rate ≤40 bpm.

Premature Beats

- APCs
  - Usually asymptomatic to the patient.
  - Characterized by premature P waves with an axis and morphology different from the sinus P waves.
  - Usually occur with normally conducted QRS complexes.
  - If wide beats are also noted, the apparently prolonged QRS beats are likely to be aberrant APCs.
    - Premature atrial and ventricular contractions rarely occur together, especially in the newborn period.
  - Slowing of the heart rate with blocked atrial bigeminy in a neonate or an infant who is dependent on adequate heart rate for normal cardiac output may alter feeding and arousal time.
- PVCs
  - Benign if
    - No evidence for heart disease.
    - QTc is normal (≤0.44 seconds).
    - Family history is not adverse.
    - PVCs are uniform in appearance.
    - PVCs are either suppressed or not aggravated with exercise.

- Worrisome if
  - Answer to any of the previous questions is positive.
- New appearance of PVCs in the setting of a febrile illness should raise the question of myocarditis.

SVT

- May be noted incidentally
- Commonly associated with signs and symptoms of congestive heart failure
  - Tachycardia
  - Tachypnea
  - Dyspnea
  - Truncal diaphoresis
  - Diminished pulses
  - Pallor
  - Hepatomegaly
  - Poor feeding
  - Palpitations
  - Chest pain
  - Nausea
  - Respiratory distress
  - Syncope (rarely)
- Neonates and infants
  - 25% of infants are in congestive heart failure with tachycardia of 24 hours' duration.
  - 50% of infants have heart failure after SVT for 48 hours.
- Children >5 years
  - Usually can communicate their distress soon after onset of SVT
  - Hence, the relative rarity of congestive heart failure caused by SVT in older pediatric patients
- Duration
  - Ranges from a few seconds to several hours
- Heart rate
  - Infants: 230–300 bpm but usually between 260–280 bpm
  - Older patients: 180–240 bpm

Atrial Flutter

- Newborns
  - Atrial rate typically between 350 and 500 bpm.
  - 2:1 AV block, means ventricular rate typically ~200 bpm.
  - Congestive heart failure tends to be less severe than in SVT.
  - Structural cardiac problems are uncommon.
- Onset in utero
  - Fetal hydrops may develop.
- IART
  - Slower atrial rate.
  - Heart rate of 100–140 bpm in a patient with risk factors should prompt investigation.

VT

- Signs and symptoms.
  - Rate >120 bpm or 25% faster than sinus rate
  - Congestive heart failure
  - Chest pain
  - Dyspnea
  - Palpitations
  - Fatigue
  - Reduced exercise capacity
  - Pallor
  - Presyncope
  - Syncope
- VT is confirmed by the presence of AV dissociation.
  - Similar but isolated PVCs and fusion beats in sinus rhythm assist in establishing the diagnosis.
  - Cardiac output frequently is compromised to a greater degree than in SVT.
  - Heart rate may be extremely rapid (≤500 bpm) and slightly irregular.
  - All wide QRS tachycardias should be considered VT until proven otherwise.
- Accelerated ventricular rhythm.
  - ≤120 bpm, or <25% faster than the basic sinus rate
  - Benign when it occurs in an otherwise normal heart

Conduction Abnormalities

- First-degree AV block
  - Prolongation of the PR interval beyond the upper limit of normal for age, with all impulses conducted
  - Seen with
    - Congenital cardiac malformations (especially AV septal defects)
    - Electrolyte disorders
    - Rheumatic fever
    - Myocarditis
    - Congenital muscular disorders
    - Patients receiving antiarrhythmic drugs
- Second-degree AV block
  - Type I
    - Progressive prolongation of the PR interval until a dropped ventricular beat (nonconducted P wave) occurs
    - Generally benign unless syncope occurs

- Normal finding in
  - Healthy children during sleep
  - Highly conditioned athletes at rest
- Type II
  - Intermittent loss of AV conduction without preceding lengthening of the PR interval
  - Implies an abnormal conduction system
- CAVB
  - No atrial impulses are conducted to the ventricles.

Sudden Cardiac Death

- Exertion or emotional stress triggers one of the following symptoms:
  - Syncope
  - Atypical seizures
  - Cardiac arrest
- Long QT3 subtype events
  - Predominantly occur at rest.
  - Physical examination is usually normal.
  - Bradycardia may be the only sign.

DIFFERENTIAL DIAGNOSIS

- Premature beats
  - Escape or late beats occurring when higher pacemaker cells fail to produce an impulse at the expected interval
- VT
  - SVT with persistent aberrancy is uncommon.
  - SVT with antegrade conduction across an accessory pathway is uncommon.
- LQTS
  - Electrolyte abnormalities
    - Hypokalemia
    - Hypocalcemia
    - Hypomagnesemia
  - Myocardial ischemia or injury
  - Acute central nervous system events
  - Cardiomyopathy

IMAGING

- Echocardiography
- Used to assess cardiac structure and function when new PVCs are seen in the setting of a febrile illness where underlying disease may be subtle
- Used in SVT to identify
  - Subtle congenital cardiac defects in patients with WPW syndrome
  - Ebstein anomaly of the tricuspid valve
  - Levo-transposition of the great vessels

DIAGNOSTIC PROCEDURES

12-Lead Electrocardiography

- Must be obtained when an arrhythmia is suspected.
  - Rhythm alterations may be quite subtle and not always identified on a rhythm strip.
  - Electrocardiography (ECG) will detect chamber enlargement.
  - Calculate corrected QT interval.

$$QTc = \frac{\text{QT interval (seconds)}}{\text{preceding RR interval (seconds)}}$$

- Analyze arrhythmia in an organized fashion.
  - Is the rhythm fast or slow?
  - Is the rhythm regular or irregular?
  - Are the QRS complexes narrow or wide?
  - What is the relationship between the P waves and the QRS complexes?
- Sinus bradycardia.
  - Neonates and infants: <100 bpm, awake
  - Children to 3 years: <100 bpm
  - Children 3–9 years: <60 bpm
  - Adolescents 9–16 years: <50 bpm
  - Adolescents >16 years: <40 bpm
- APCs.
  - If APC occurs when one of the bundle branches is refractory
    - The premature beat will be conducted down the other bundle branch.
    - The result is an aberrant APC with QRS morphology wider than and different from sinus QRS complexes.
  - If both bundle branches are refractory
    - APC will not be conducted to the ventricles (blocked APC).
    - APC may reset the sinus node, with a resultant pause greater than the previous RR interval.
  - T waves
    - Usually smoothly inscribed.
    - Consistent sharp deflections in the T waves may represent P waves.
- Wandering atrial pacemaker related to alterations in vagal tone.
  - Usually noted with slower heart rates and characterized by different P wave morphologies
- QRS morphology of PVCs.
  - Different from sinus QRS beats.
  - Occur before the next expected sinus beat.
  - Not preceded by a premature P wave.
  - QRS duration may be only slightly prolonged.
  - Uniform PVCs.
    - Similar morphology to one another

- Multiform PVCs.
  - Diverse morphology
- Late PVCs.
  - Hybrid or fusion beat with morphology intermediate between the sinus QRS and PVC

- SVT.
  - QRS complexes are usually narrow but may be transiently wide at initiation.
  - Wide QRS tachycardias should be considered ventricular in origin until proven otherwise.
  - Careful attention should be paid to the T waves for sharp deflections representing retrograde conduction from the ventricles to the atria via an accessory pathway.
  - WPW syndrome warrants further (echocardiographic) investigation.
    - Higher incidence of defects (eg, hypertrophic cardiomyopathy, Ebstein anomaly, levo-transposition of the great vessels)
- Atrial flutter.
  - Newborns
    - Rapid sawtooth pattern with inverted P waves in the inferior limb leads
  - Atypical form (IART)
    - Distinct P waves separated by isoelectric periods
- VT.
  - QRS complexes differ from the sinus QRS complexes.
    - Typically wide
    - Young infants are an exception; minimal QRS prolongation (0.08–0.09 seconds) may be seen.
- Sudden cardiac death.
  - Marked prolongation of QTc intervals
  - QTc interval >460 milliseconds = LQTS
  - QTc interval 440–460 milliseconds = borderline
- During administration of adenosine.
  - Detect rare conversion to a more malignant arrhythmia.
  - Once conversion to a sinus rhythm is achieved, 12-lead ECG should be repeated to look for evidence of preexcitation.

Ambulatory (Holter) Monitoring

- Criteria for diagnosis of sinus bradycardia
  - Neonates and infants: <60 bpm, sleeping; <80 bpm, awake, quiet
  - Children 2–6 years: <60 bpm
  - Children 7–11 years: <45 bpm
  - Adolescents >11 years: <40 bpm
  - Athletes: <30 bpm

TREATMENT APPROACH

- Empirical therapy without detecting arrhythmia does not meet the current standard of practice.
- Depending on clinical and nonclinical factors
  - No therapy
  - Drug therapy
  - Ablation
  - Pacemaker

SPECIFIC TREATMENT

Premature Beats

- APCs
  - Therapy not necessary unless
    - APCs initiate SVT.
    - APCs block impulses in a newborn dependent on heart rate to maintain adequate cardiac output.
  - If suppressive therapy is required
    - Digoxin
    - Propranolol
- PVCs
  - Neither treatment nor curtailment of exercise is required, even if a bigeminal rhythm is present.
  - If worrisome PVCs are present, the need for therapy should be determined by a pediatric cardiologist.

SVT

- Young children
  - Cardiogenic shock
    - Direct current synchronized cardioversion
    - Adenosine
      - Administered via intravenous (IV) bolus of 100 mcg/kg, if venous access is available.
      - Follow with a second doubled dose if the first dose is ineffective.
      - Should be administered with ECG monitoring.
    - Procainamide
      - Use if adenosine is ineffective or if SVT quickly recurs.
      - Can be administered intravenously to infants and young children after appropriate loading, with a subsequent repeat trial of adenosine.
  - IV verapamil and propranolol
    - Suppressive therapy with propranolol is appropriate in WPW syndrome.
    - These agents are contraindicated in infants <1 year.

- Digoxin and verapamil
  - Should be avoided in WPW.
  - May shorten the antegrade refractory period of the accessory pathway, allowing more rapid conduction to the ventricles.
  - Potentially fatal if atrial fibrillation develops.
  - If preexcitation is not present, either agent can be used to prevent recurrence.
  - Many cardiologists avoid the use of digoxin because of concerns about unproven efficacy and potential toxicity.
- β-blockers
  - Not universally effective and may aggravate congestive heart failure, sick sinus syndrome, or bronchospasm
- Other medical therapies
  - Use if the previous agents are ineffective.
  - All require hospitalization for drug initiation because of possible proarrhythmic effect
    - Flecainide
    - Sotalol
    - Amiodarone
- Ablation
  - Not recommended during the first 2 years of life
    - Resultant myocardial scar may grow with the patient and become a subsequent nidus for malignant, often drug-refractory arrhythmias.

- Older children and adolescents
  - Therapeutic choices depend on
    - Frequency
    - Ease of conversion of episodes
  - No therapy other than self-conversion via a Valsalva maneuver or headstand
  - Drug therapy with consideration of
    - Duration
    - Compliance
    - Cost
  - Radiofrequency ablation
    - ≥90% successful but with a chance of a later recurrence.
    - If the patient with SVT will undergo surgery for a cardiac defect, preoperative assessment and ablation should be considered to reduce arrhythmia-related postoperative morbidity and potential mortality.

Atrial Flutter

- In newborns, spontaneous conversion may occur within a few hours of birth.
- Electrical cardioversion.
  - Required in most
- Chronic pharmacotherapy.
  - Usually unnecessary because recurrences are rare

VT

- Acute management
  - Depends on the patient's clinical status
    - Rate and duration of VT
    - Presence of structural cardiac lesions
    - Prior myocardial dysfunction
  - Hemodynamic compromise
    - Electrical cardioversion with 1–2 watt-seconds/kg
  - If reasonable clinical stability is present
    - IV amiodarone
    - Procainamide
    - Magnesium
    - Lidocaine
- Long-term suppressive therapy
  - Predicated on
    - Risk of recurrence
    - Morbidity and mortality of the type of VT
    - Risk to benefit ratio of treatment
  - Common antiarrhythmic agents to prevent VT recurrence
    - β-blockers
    - Sotalol
    - Amiodarone
  - Other treatments
    - Implantation of an automatic cardioverter-defibrillator
    - VT ablation
- Benign forms of VT
  - Accelerated ventricular rhythm
    - Requires observation only
  - Right ventricular outflow tract tachycardia

Conduction Abnormalities

- First-degree AV block
  - Usually benign in most settings
- Second-degree AV block
  - Type I
    - No therapy is required in most cases.
  - Type II
    - Ongoing medical surveillance
    - Potential need for pacemaker implantation

- CAVB
  - Early pacemaker implantation is advised in neonates and infants with
    - Risk factors
    - Symptoms of inadequate cardiac output
  - Isoproterenol
    - Infuse if necessary to increase the heart rate while awaiting pacemaker therapy.
    - Should not delay implantation.
  - If not in infancy, pacemaker insertion in adolescence is usually necessary depending on
    - Symptoms
    - Ventricular rate
    - Stability of the ventricular escape rhythm

Sudden Cardiac Death

- LQTS
  - β-blocker therapy
  - Restriction from competitive sports
  - Invasive management options include
    - Cardiac pacing
    - Left stellate ganglionectomy
    - Implantation of internal cardiac defibrillator
  - Avoidance of
    - Sympathomimetics
    - Drugs capable of prolonging the QTc
    - Rapid correction of electrolyte abnormalities
  - For child or adolescent who collapses suddenly with no discernible cardiac output
    - Rapid resuscitation, including early defibrillation

WHEN TO REFER

- Arrhythmias associated with presyncope, syncope, chest pain, or a sense of doom
- Arrhythmias associated with repaired or unrepaired congenital heart disease or cardiomyopathies
- Family history of premature (<35 years) sudden cardiac death
- Persistent or repetitive bradycardias or tachycardias
- Premature ventricular beats that increase with exercise
- Asymptomatic WPW syndrome
- Mobitz type II AV block for ongoing cardiac surveillance and potential pacemaker

WHEN TO ADMIT

- Arrhythmias associated with congestive heart failure, syncope, or low cardiac output
- Symptomatic high-grade AV block
- Difficult-to-control SVT, atrial flutter
- VT
- Heart disease with syncope, aborted sudden death

FOLLOW-UP

- Premature beats
  - Frequent PVCs
    - Long-term yearly follow-up.
    - Watch for arrhythmia-induced ventricular dilatation.
    - Watch for ventricular dysfunction.
- SVT
  - Neonates and infants should be observed after treatment in view of the risk of later recurrence.

PROGNOSIS

- SVT
  - SVT onset during the first 4 months of life
    - 60% will have recurrences.
    - >90% will be free of clinical episodes of tachycardia by 1 year of age.
      - As many as one-third of these children may have a recurrence at a mean age of 8 years.
  - SVT onset at ≥5 years
    - Chance of recurrent episodes of tachycardia is 75%–80%.
  - WPW syndrome/preexcitation
    - Small but definite where there is no SVT (0.05%–0.50% per year) risk of sudden death.
    - With tachycardia there is substantially increased risk for sudden death.
  - Automatic ectopic tachycardias
    - Often incessant and relatively drug resistant.
    - Tachycardia-induced cardiomyopathy is possible if conversion is not achieved.
- Atrial flutter
  - Atypical form
    - If conversion to and maintenance in a sinus rhythm cannot be achieved, morbidity is substantial, with a 4- to 5-fold increase in risk for sudden death.
- VT
  - Benign forms
    - Substantial incidence of spontaneous resolution in childhood
- Conduction abnormalities
  - Second-degree AV block
    - Type I: little risk of progression to complete block.
    - Type II: Progression to higher levels of AV block occurs.

- CAVB
  - 20% mortality risk
- CCAVB
  - 75% mortality rate even with permanent pacing

- Sudden cardiac death
  - Annual mortality after onset of symptoms in untreated young patients
    - 1%–5%
    - Nearly 10% risk of sudden death as the initial symptom
  - Highest risk for sudden death in patients with
    - History of syncope
    - QTc more than 500 milliseconds
  - LQTS
    - Cumulative probability of a cardiac event (predominantly syncope) in patients who are genotyped LQT1, 2, and 3 by 15 years of age
      - 10% LQT3
      - 69% LQT1
    - Jervell and Lange-Nielsen syndrome
      - Substantially higher incidence of sudden death compared with Romano-Ward syndrome variant
    - Rarely, may be a cause of SIDS

PREVENTION

- Conduction abnormalities
  - LQTS
    - Automatic external defibrillators.
      - Availability in some school systems has already begun to decrease the incidence of sudden cardiac death in the young.
    - Risk may be stratified by asking 2 critical questions in pre-sports clearance evaluations.
      - Has the patient ever passed out, had visceral chest pain, or experienced symptomatic palpitations during strenuous exercise?
      - Has any family member died suddenly and unexpectedly before the age of 35 years?
      - An affirmative answer to either question should prompt a cardiologic referral before participation in competitive sports.

Cerebral Palsy

DEFINITION

- *Cerebral palsy* (CP) is a clinical descriptive term for a continuum of disorders of movement, posture, and coordination caused by a variety of static conditions affecting the brain.
  - Motor disorder often accompanied by disturbances of any of the following functions, alone or in combination:
    - Sensation
    - Cognition
    - Communication
    - Perception
    - Behavior
  - Can also be accompanied by a seizure disorder
  - Can include impairment in the musculoskeletal system, most commonly
    - Contractures (eg, equinus deformity)
    - Torsional changes in long bones (eg, femoral and tibial torsion)
    - Joint instability (eg, hip displacement)

SIGNS AND SYMPTOMS

- Although the brain lesion or anomaly, once recognized in early childhood, is no longer progressive, clinical signs change, especially in the first several years of life.
  - Abnormal patterns emerge as the damaged nervous system matures.
    - For example, a child destined to have spastic quadriplegia
      - Is often hypotonic in early infancy.
      - At 6 months, may develop adduction of the thumb (palmar thumb).
      - Followed in 1–2 months by scissoring of the legs when held upright.
      - By 9 months, may have diffuse spasticity and hyperactive deep-tendon reflexes.
      - Dyskinetic patterns may not be obvious until ~18 months.
      - Ataxia may be apparent even later.
- Early signs.
  - Difficulty feeding because of abnormal oral-motor patterns
    - Tongue thrusting
    - Tonic bite
    - Oral hypersensitivity
  - Irritability
  - Delayed milestones, such as head control

DIFFERENTIAL DIAGNOSIS

Possible Diagnoses

- Neurodegenerative disorders
- Inborn errors of metabolism
  - Some rare inborn errors of metabolism (arginase deficiency and glutaric aciduria) may mimic CP.
  - These cause progressive deterioration, whereas CP does not.
- Developmental or traumatic lesions of the spinal cord
- Severe neuromuscular disease
  - Hypotonia in association with weak muscles and depressed tendon reflexes suggests a neuromuscular disease.
  - Many children with spastic and extrapyramidal CP are hypotonic in early infancy.
- Movement disorders
- Spinocerebellar degeneration
  - Repeated examinations are necessary to rule out a progressive degenerative condition.
- Neoplasms
- Hydrocephalus
- Subdural hematoma
- Dopa-responsive dystonia
  - Rare but treatable form of dystonia.
  - May begin with toe walking and difficulties with gait.
  - Responds dramatically to administration of levodopa.
  - In most instances, no history can be found of a preexisting condition consistent with CP.
- Hereditary spastic diplegia
  - Consider in a child with a parent who has CP and has late-onset spastic diplegia with no preceding history of prenatal or neonatal problems.

Categorization by Type, Distribution, and Severity of Motor Abnormality

- CP can be simplified into 3 categories.
  - Spastic (involving the pyramidal tracts)
  - Dyskinetic (involving the extrapyramidal tracts)
  - Mixed (involving both)
- Spastic CP
  - Associated with neurologic signs, including
    - Hyperreflexia
    - Clonus
    - Extensor plantar response
    - Contraction of muscles
    - Persistent primitive reflexes
    - Abnormal postural control

- Abnormalities impair normal movements, such as gait and manipulation of objects, in complex ways.
  - Movement is often stiff, with frequent abnormal patterns, such as fisting of hands, retraction of shoulders, scissoring of legs, and toe walking.
  - Hypotonia of the trunk and neck is common.
- 3 types of spasticity.
  - Diplegia
    - The legs are affected with relative sparing of the arms.
    - Children with hydrocephalus are more likely to develop spastic diplegia.
  - Quadriplegia
    - All 4 limbs are significantly and functionally impaired, with the legs more severely involved than arms.
    - More likely to have intellectually disabilities (64% have an IQ <50) and have seizures (56%).
    - More likely to have feeding difficulties, severe joint contractures, and scoliosis.
  - Hemiplegia
    - Only one side is involved, with the arm usually more impaired than the leg.

- Dyskinetic CP
  - Dyskinesia includes the involuntary movements of athetosis, chorea.
  - Dystonia.
    - Sustained muscle contractures that lead to abnormal posture and twisting
  - Ataxia.
    - Incoordination of movement and impaired balance; may be associated with an intention tremor

DIAGNOSTIC APPROACH

- A direct link, if successfully identified, between the type of CP and its cause requires diagnostic evaluation.
  - Cranial ultrasonography
  - Magnetic resonance imaging (MRI)
- The mean age at which CP is diagnosed is 10 months.
  - Therefore, in addition to formal developmental screening recommended for all children, those at risk for CP should have
    - Regular careful physical examinations
    - Special attention to neurologic status
- Early diagnosis is aided by
  - History of abnormal pregnancy, labor, delivery, or neonatal period
  - Report of serious acute illness and trauma
- Should evaluate
  - Primitive reflexes
  - Postural responses
  - Muscle tone (atypical)
  - Motor milestones
  - Neurobehavioral responsiveness
- Screening for metabolic and genetic disorders is not recommended unless the child has atypical features, such as unusual facial features, or a progressive condition.
- Chromosomal disorders and inborn errors of metabolism
  - Can be misdiagnosed as atypical CP.
  - Genetic evaluation may be diagnostic when CP remains unexplained.

IMAGING

- Neuroimaging techniques may aid in understanding of structural abnormalities and timing of lesions.
  - Ultrasonography
  - Computed tomography
  - MRI
- Neuroimaging may demonstrate
  - Periventricular leukomalacia
  - Postischemic necrosis
  - Cerebral dysgenesis
  - Hydrocephalus
  - Porencephaly
  - Tumor
  - Prenatal ischemic injury
  - Leukodystrophy

DIAGNOSTIC PROCEDURES

- Electroencephalography
  - Important part of diagnosis and management of associated seizures
    - Continuous electroencephalographic monitoring with videography may help differentiate seizures from other movement disorders.
  - Not helpful in diagnosis of CP
- Evaluation of altered gait and feeding disorders may require special diagnostic studies.
  - Gait analysis
    - Using videography, electromyography, and sensors
    - Has improved orthopedic care
  - Video-fluoroscopic swallowing studies

CLASSIFICATION

- Gross motor function classification system
- Most common system for classifying severity
  - 5-level system to classify severity of motor involvement based on functional abilities and need for assistive technology and wheeled mobility

TREATMENT APPROACH

- Goals are for the patient to be as independent as possible and to participate in family and community activities with unaffected peers.
  - Try to identify opportunities for participation.
  - Encourage child to engage in any and all activities that are available.
- Multiple interventions are possible.
  - Muscle strengthening
  - Orthotics (eg, ankle-foot orthoses)
  - Oral medication
  - Botulinum toxin injections (with or without serial casting)
  - Intrathecal baclofen pump
  - Selective dorsal rhizotomy
  - Orthopedic surgery
- The best approach requires input of child and family with a team of clinicians (therapists, orthotists, surgeons, nurses, physicians, and social workers).
- Families often turn to alternative therapies.
  - The primary care physician should inquire about them and be aware of
    - Their nature
    - Possible interactions with medications
    - Potential for harm
- The 3 most important issues for adults with CP are
  - Communication skills
  - Self-care
  - Mobility
- Interventions (eg, medications, surgery, braces, adaptive equipment) should focus on these issues.

SPECIFIC TREATMENTS

Medications

- Oral medications can reduce spasticity but have potential adverse effects, and evidence for functional benefits is limited.
  - Diazepam
  - Baclofen
  - Tizanidine
  - Dantrolene
- Intramuscular botulinum toxin is effective in children with functional spasticity by transiently reducing spasticity in individual limbs.
- Drooling can be treated with
  - Scopolamine (transdermal patch or tablet)
  - Glycopyrrolate
  - Botulinum toxin injections into salivary glands

Surgical Procedures

- Selective dorsal rhizotomy and intrathecal baclofen reduce spasticity and increase range of motion.
- Orthopedic procedures, such as tenotomies, tendon releases, and transfers, address soft-tissue and bone problems.
- Drooling may be managed with surgical removal of the salivary glands.

Physical Modalities

- Constraint therapy produces anatomic changes in the brain on functional MRI.
  - Cannot improve selective motor control, difficulties with balance, and weakness.
  - Immobilizing the better upper extremity in children with hemiplegia while providing therapy to enhance the function of the affected limb and hand improves function.
- Strength training can improve function.
- Casting and splinting techniques to maintain muscle length and inhibit increased tone may be helpful.
- After orthopedic surgery, therapy should be started to maximize range of motion and skills.

Assistive Devices

- To assist motor activities.
  - Switches that improve ability to control the environment
  - Computers
  - Small electric motors
- Communication augmentation.
  - Speech synthesizers
  - Symbol charts
  - Spelling boards
- Simple enhancements to improve quality of life.
  - Ramps
  - Accessible showers
  - Assistive devices, such as a pencil holder or mouth-activated switch
- The Individuals With Disabilities Education Act (IDEA) requires that school-aged children with disabilities be assessed for the utility of assistive devices and be given the support needed to use them effectively.

- Gaining access to these services requires
  - Coordination of care
  - Knowledge of the resources available in the community
  - Referral to experts
  - Financial assets
- The physician is obliged to ensure that these services are available to the patient and the family.
- See **Table 1** for approaches to specific disabilities and impairments.

Alternative Treatments

- The following alternative treatments may offer functional benefits:
  - Equine-assisted therapy (hippotherapy)
  - Acupuncture
- Hyperbaric oxygen
  - No evidence to support use and associated with risk of increased seizures and trauma to tympanic membranes
- Electrical stimulation
  - Evidence for effectiveness is lacking.

WHEN TO ADMIT

- Children who aspirate food or saliva or have inadequate nutrition
  - Demonstrate increased susceptibility to acute illnesses (eg, pneumonia).
  - Should be hospitalized if severely ill or cannot be managed at home.

WHEN TO REFER

- In United States, all infants and children <3 years with CP should be referred to an early intervention program.
  - Mandated under IDEA.
  - Special education.
  - Physical, occupational, and speech therapies.
  - Adaptive equipment.
  - Training for mobility and living skills.
  - Communication.
  - Therapies may not change the basic disorder significantly.
    - However, therapists may help the families.
      - Teaching them how to position and handle their child
      - Providing more opportunity for play and learning
      - Facilitating feeding and the parent-child relationship
- Children with moderate or severe CP
  - Should be referred to an interdisciplinary clinic, if available
    - If not, referral to an orthopedist, physical therapist, and health care practitioner (developmental pediatrician, neurologist, pediatric rehabilitation specialist) who can manage spasticity and other abnormalities of tone and optimize functioning
- Children with seizures should be referred to a neurologist.
- Gastroenterologist or aerodigestive clinic for children who might benefit from enteral feeding.
- The primary care physician should coordinate referrals.
  - Ensure that the child is receiving coordinated, comprehensive care.
- The family should have early professional support to help them cope with the crisis of diagnosis.

FOLLOW-UP

- Careful monitoring of physical growth is critical.
  - Monitoring weight for length rather than weight alone is important.
  - Reliable measures are often impossible to obtain.
    - Tibial length is used as a proxy for height.
- Long-term planning and preparation are required to help children make the transition from adolescence to adulthood, particularly when the child has multiple needs.

COMPLICATIONS

- Osteoporosis.
  - Common in patients with severe quadriplegia and immobility
- Impaired self-care/hygiene.
  - Due to gross motor and fine-motor abnormalities and associated conditions, such as drooling
- Dental disease.
- Inhibited physical growth.
- Failure to thrive.
  - Especially those with dyskinesia or spastic quadriplegia.
  - Feeding difficulties/recurrent vomiting may be associated with aspiration.
- Language abnormality (from aphasia to poor articulation).
- Specific learning disabilities, such as visuospatial impairment, are common in a child with a normal range of intelligence.

C

Table 1. Disabilities and Impairments Associated With Cerebral Palsy in Children and Possible Interventions

Disability or Impairment	Possible Intervention	Possible Consultation
Impaired communication	Augmentative communication aids	Speech therapist, audiologist
Impaired cognition	Early intervention, special education program, formal educational testing	Education specialist, psychologist, school advocate
Weakness or impaired mobility	Orthoses (braces), walker, wheeled mobility and strength training, hippotherapy Constraint therapy for hemiplegia	Orthopedist, orthotist, physical therapist Physical therapist specialty program, gait laboratory Hippotherapist Occupational therapist
Spasticity	Medications, selective dorsal rhizotomy, intrathecal baclofen, botulinum toxin injections	Orthopedist, neurodevelopmental specialist, physiatrist, neurologist, neurosurgeon
Joint contractures	Range of motion, orthoses, surgery	Physical therapist, orthopedist, orthotist
Scoliosis	Orthoses, surgery	Orthopedist, orthotist
Impaired self-care and hygiene	Assistive technologic devices, home modifications, training	Occupational therapist, rehabilitation engineer
Drooling	Scopolamine patch, glycopyrrolate, surgery, botulinum toxin injections, acupuncture	Otolaryngologist, acupuncturist
Sexual functioning	Education, adaptive devices	Gynecologist, urologist, psychologist
Impaired nutrition or feeding	Education, monitoring, medical evaluation, medication, enteral routes of feeding	Dietitian, gastroenterologist, speech therapist, occupational therapist, surgeon
Dental caries, malocclusion	Repair of dental caries, orthodontics	Dentist, pedodontist, orthodontist
Seizures	Medication, surgery	Neurologist, neurosurgeon
Impaired vision or hearing	Assistive devices, surgery	Ophthalmologist, otolaryngologist
Adverse effects on family	Parent support group, counseling, support, respite	Social worker, psychologist, specialty program, care coordinator
Impaired transition to adulthood	Counseling, adult-oriented health care, care coordination, transportation, recreation, vocational services, financial planning, guardianship	Internist, family physician, care coordinator, vocational specialist, independent living specialist, attorney, psychologist, financial planner

- Cognitive impairment (75% of cases).
  - Learning disabilities in ~40%
  - Epilepsy in 35%
  - Visual impairments in 20%
  - Infantile hydrocephalus in 9%
- Impaired mobility.
- Impairment in gastrointestinal functioning.
  - Drooling in 31%
  - Dysphagia in 19%
  - Constipation in 25%
- Impairment in growth.
- Behavioral problems.

PROGNOSIS

- Survival depends on the severity of CP.
  - A 2-year-old with severe CP is expected to have a 40% chance of living to age 20 years.
    - A child with mild CP has a 99% chance.
  - Life expectancy is lower for those with more severe limitations in motor function and feeding skills.
- Greatest risk for early death if child has all of the following symptoms:
  - Intellectual disability
  - No independent mobility (ie, rolling), limited spontaneous movement
  - Can be fed only by gastronomy tube
- Prognostication before child's second birthday may be difficult, except at the extremes of involvement.
- Prognosis for functioning is related to
  - Clinical type of CP
  - Pace of motor development
  - Evolution of infantile reflexes
  - Intellectual abilities
  - Sensory impairment
  - Emotional-social adjustment
- Prognosis for walking.
  - Patients who sit unsupported by 24 months and crawl by 30 months are more likely to walk independently.
  - Retention of obligatory primitive reflexes at 18 months of age makes independent ambulation unlikely.
  - Virtually all with hemiplegia learn to walk, as do many with dyskinesia or ataxia.
- Individual achievement is related to many factors.
  - Intelligence.
  - Physical functioning.
  - Ability to communicate.
  - Personality attributes.
  - Major factors in adjustment as adults.
    - Availability of training, jobs, sheltered employment
    - Counseling
  - A supportive family and availability of specialist medical care are other important factors.

PREVENTION

- Prevention of preterm birth
- In some instances, CP may be prevented by
  - Reducing occurrence of injuries during childhood
  - Minimizing periventricular leukomalacia in preterm neonates
    - Improving circulation
    - Countering effects of excitatory neurotransmitters (eg, head cooling in newborn who has had a hypoxic or ischemic event)

Chest Pain

DEFINITION

- *Chest pain* is defined as discomfort in the thoracic region.

HISTORY

- A detailed history includes
  - The child's response to the pain
    - If possible, children should describe the pain in their own words.
    - They should be asked what they think is causing the pain.
  - Location, duration, radiation, and quality of the pain
  - Aggravating and alleviating factors
  - Any associated signs and symptoms
  - Any history of trauma, even if it occurred 1–3 months earlier
- To many adolescents, chest pain is synonymous with heart disease; therefore, this issue should be addressed.
  - If no cardiac cause is discovered, the physician should unequivocally explain to the adolescent and the family that the heart is normal.
- The quality of pain can help determine its source.
  - Deep, poorly localized pain that radiates to the neck or shoulders is characteristic of visceral pain.
  - Superficial sharp pain that is exacerbated by lifting or movements of the torso suggests musculoskeletal pain.
  - Peripheral pain that increases with inspiratory efforts originates from pleural inflammation.
  - Sharp pain that decreases when the child leans forward is characteristic of pericardial inflammation.
  - Pain that occurs with exercise points toward respiratory or cardiac conditions.
  - Pain that awakens the child from sleep is never psychological.
- Common, uncommon, and rare causes of chest pain and associated signs and symptoms.
  - Musculoskeletal
    - Costochondritis (common): localized, superficial, reproducible pain over costochondral junction
    - Exercise, overuse, muscle strain (common): reproducible pain with use of involved muscle group
    - Protracted coughing or vomiting (common): intercostal muscle tenderness
      - Trauma: localized pain; pain with movement of involved areas
      - Stitch (common): sharp, crampy costal pain that occurs with running
      - Precordial catch (uncommon): transient, stabbing pain at left sternal border; relieved by forced inspiration
  - Pulmonary
    - Asthma (common): associated with cough, shortness of breath, wheezing, abnormal pulmonary function tests; relief with inhaled bronchodilators
    - Exercise-induced bronchospasm (common): abnormal findings on exercise tests; improvement with bronchodilators
    - Pneumonia (common): crackles, fever, cough
    - Pleural effusion (uncommon): pleural rub, fever, decreased breath sounds
    - Pneumothorax (uncommon): sudden pain, referred shoulder pain, dyspnea
    - Pulmonary embolus (rare): contraceptive use or recent abortion, pleuritic pain
  - Gastrointestinal
    - Esophagitis (common): retrosternal pain; relief with antacids
    - Gastroesophageal reflux (common): retrosternal burning pain; worse after eating and when reclining; relief with antacids
  - Cardiac
    - Hypertrophic cardiomyopathy (rare): syncope, family history, systolic ejection murmur
    - Pericarditis (rare): associated fever with acute onset of pain; pain increases with movement; narrow pulse pressure, distant heart sounds; alleviated by leaning forward
    - Myocarditis (rare): precedent viral illness, anorexia, shortness of breath, third heart sound or gallop, cardiomegaly
  - Emotional
    - Psychogenic (common): normal physical examination, trouble sleeping, family or school problems, life stresses, family history of chest pain, other somatic symptoms
    - Hyperventilation (common): associated light-headedness, paresthesias, underlying anxiety

PHYSICAL EXAMINATION

- Findings that suggest musculoskeletal and chest wall conditions.
  - Signs of trauma, such as bruising.
  - Swelling over joints.
  - Splinting or an abnormal breathing pattern.
  - Reproduction of point tenderness at the origin of the spontaneous pain is the strongest evidence favoring the diagnosis of chest wall disease.
    - Each rib cartilage should be palpated with only one finger or with the child's finger.
  - Pain from the thoracic cage that can be elicited by movements of the torso or by flexion of the arms is highly suggestive of a musculoskeletal chest wall injury.
- Findings that suggest a parapneumonic effusion.
  - Fever, tachypnea, tachycardia, pleural friction rub and/or crackles, and dullness to percussion
- Findings that suggest a spontaneous pneumothorax.
  - Dyspnea, shoulder pain, and tachypnea
- Findings that suggest a cardiac source.
  - Any new clicks, rubs, or systolic murmur or change in a previous murmur
- Findings that suggest myocarditis or pericarditis.
  - An ill appearance, fever, dyspnea, changes in the pain associated with the respiratory cycle.
  - A third heart sound or gallop can be heard in myocarditis and congestive heart failure.
- Findings that suggest a hyperventilation syndrome.
  - Carpopedal spasm
  - Paresthesias
- Adolescents with gynecomastia or breast pain may experience chest pain that is easily discernible on inspection and palpation of the developing breast tissue.

DIFFERENTIAL DIAGNOSIS

Musculoskeletal Conditions

- Costochondritis
- Exercise, overuse, muscle strain
- Protracted cough or vomiting
- Trauma
- Stitch
- Precordial catch (uncommon)

Pulmonary Conditions

- Asthma
- Exercise-induced bronchospasm
- Pleural effusion (uncommon)
- Pneumothorax (uncommon)
- Pulmonary embolus (rare)

Gastrointestinal Conditions

- Esophagitis
- Gastroesophageal reflux

Cardiac Conditions

- Hypertrophic cardiomyopathy (rare)
- Pericarditis (rare)
- Myocarditis (rare)
- Nonorganic
- Psychogenic
- Hyperventilation

LABORATORY EVALUATION

- Screening laboratory tests are usually not helpful in establishing a specific diagnosis.
- A thorough history and physical examination should guide the clinician in ordering tests.

IMAGING

- In most cases, chest radiographs will only confirm what is suspected clinically.
- A chest radiograph is indicated if the clinician suspects
  - Pneumothorax
  - Pericarditis
  - Pneumonia
  - Pleural effusion
  - Other pulmonary disease

DIAGNOSTIC PROCEDURES

- In most cases, electrocardiography will only confirm what is suspected clinically.
- If the pain occurs with exercise, exercise testing or spirometry may help uncover underlying asthma or exercise-induced bronchospasm.
- To confirm the diagnosis of exercise-induced or cold air–induced bronchospasm
  - Exercise testing
  - Cold air challenge
  - A therapeutic trial of bronchodilators

TREATMENT APPROACH

- It is important to define whether the chest pain is secondary to an underlying physical abnormality, psychogenic, or idiopathic.
- Treatment of psychogenic chest pain should be focused on
  - The family's understanding of the cause of the pain
  - Reassurance that no long-term sequelae exist
  - Acknowledging that the pain is real to the child

- Children with idiopathic chest pain may benefit from a trial of antacids or histamine$_2$-blockers because the clinical presentation of esophagitis can be nonspecific.

SPECIFIC TREATMENT

- Exercise-induced bronchospasm
  - Treatment with bronchodilators will help these children participate in sports and allow them to lead normal, active lives.
- Hyperventilation syndrome
  - For a child with an acute episode, the treatment is to have the child breathe into a paper bag to relieve the hypocapnia.
  - Resolution of the chronic problem is based on techniques to allow children to understand the nature of their anxiety and regain control of their emotional state.

WHEN TO REFER

- Signs and symptoms that accompany chest pain and warrant referral or hospitalization.
  - Signs
    - History of Kawasaki disease, Turner syndrome, Marfan syndrome, sickle cell disease, or cystic fibrosis
    - Recent elective abortion, calf pain, oral contraceptive use
    - Family history of hypertrophic obstructive cardiomyopathy or unexplained syncope
    - Pica
    - Foreign body aspiration
    - Conversion disorder
    - Cyanosis or toxic appearance
    - Murmur that increases with Valsalva maneuver
    - Pleural or pericardial friction rub
    - Pulsus paradoxus
    - Cardiac clicks, thrills, gallop, or third heart sound
  - Symptoms
    - Syncope
    - Fevers, chills, weight loss, malaise, anorexia
    - Respiratory distress
    - Chest pain with exercise
    - Palpitation or tachycardia
- A pediatric cardiologist should see children with chest pain and a family history of sudden death.
- If palpitations or chest pain occurs infrequently or is not associated with exercise, referral for Holter monitoring is indicated.
- For children with more significant psychiatric problems, referral to a psychiatrist may be necessary.

WHEN TO ADMIT

- Children with chest pain rarely require hospitalization because chest pain is usually benign, self-limited, and not associated with severe intrathoracic illness.
- Children with the following conditions should be hospitalized:
  - Myocarditis
  - Pericarditis
  - Empyema
  - Pneumothorax
  - Significant thoracic trauma
  - Acute chest syndrome
  - Esophageal foreign bodies
  - Coronary artery anomalies or other cardiac lesions
  - Myocardial ischemia
  - Chest pain and palpitations
  - Cyanosis
  - Distress

FOLLOW-UP

- Patients with psychogenic or idiopathic chest pain should be followed up at regular intervals.

PROGNOSIS

- Prognosis depends on the cause of the chest pain.

Chronic Fatigue Syndrome

DEFINITION

- *Chronic fatigue syndrome* (CFS) describes an illness characterized by prolonged periods of debilitating fatigue for which no definitive cause is known.
- Although the Centers for Disease Control and Prevention has created a working definition of CFS, it is not a well-defined clinical entity.

SIGNS AND SYMPTOMS

- Primary manifestation is severe fatigue.
  - >6 months in duration
  - Limits individual to activity <50% of the premorbid level
- Associated symptoms include
  - Sore throat
  - Low-grade fever (oral temperatures of 37.5°C–38.6°C [99.5°F–101.5°F])
  - Painful lymph nodes
  - Unexplained generalized weakness, myalgias, or arthralgias (or both)
  - Prolonged fatigue after exercise
  - Headache
  - Difficulty concentrating or memory loss
  - Sleep disturbances (hypersomnia or insomnia)
- Onset.
  - Most patients describe sudden onset with an initial mononucleosis- or influenza-like illness.
  - Many describe a history of atopy, multiple allergies, or both.
- History.
  - Question the patient about the nature and duration of symptoms.
  - Identify possible exposures to ill persons that might suggest an alternative diagnosis.
  - Obtain personal and social history.
    - Family dynamics
    - Prior level of functioning
    - Response to illness
    - Family history of psychiatric illness
    - Psychological or marital problems
      - Common psychological issues include internalizing symptoms and feeling different from others.
- Physical examination, with a goal of eliminating other causes of the patient's symptoms.
  - Mild inflammation of the pharynx
  - Cervical or axillary lymphadenopathy
  - Low-grade temperature elevation in up to 50% of cases

DIFFERENTIAL DIAGNOSIS

- The following symptoms should suggest an alternative diagnosis:
  - Enlarged lymph nodes (>2 cm)
  - Weight loss >10% of body mass index without dieting
  - Focal neurologic abnormalities
- Differential diagnoses
  - Cancer
  - Autoimmune disease
  - Localized infection (eg, sinusitis, occult abscess)
  - Chronic or subacute infection (eg, Lyme disease, endocarditis, tuberculosis, mononucleosis)
  - HIV infection
  - Fungal disease (eg, histoplasmosis, coccidioidomycosis, blastomycosis)
  - Parasitic disease (eg, toxoplasmosis)
  - Chronic inflammatory disease (eg, sarcoidosis, Wegener granulomatosis)
  - Endocrine disease (eg, hypothyroidism, Addison disease, diabetes, hypoglycemia)
  - Neuromuscular disease (eg, myasthenia gravis, multiple sclerosis)
  - Drug dependency
  - Side effects of chronic medications or other toxic agents (eg, chemical solvent, heavy metal, pesticide)
  - Psychiatric disorder (eg, depression)
  - Total allergy syndrome
  - Sleep disorders or sleep deprivation

DIAGNOSTIC APPROACH

- Focus on excluding all other diagnoses and making an extensive differential diagnosis.
  - Physical examination.
  - Laboratory tests.
  - Chest and sinus radiographs.
  - Cardiologic evaluation may be useful in patients with dizziness.

LABORATORY FINDINGS

- No specific laboratory tests exist that can be used to diagnose CFS.
- Primary aim of laboratory evaluations is to eliminate other conditions.
- Suggested battery of screening tests.
  - Complete blood cell count and differential
    - Erythrocyte sedimentation rate
    - Serum electrolytes
    - Creatinine
    - Blood urea nitrogen
    - Glucose

- Liver enzyme and function tests
- Thyroid function tests
- Tuberculin skin test with controls
- Alkaline phosphatase
- Antinuclear antibodies
- Rheumatoid factor
- HIV antibody

- Additional tests (eg, Lyme disease test, viral serologies) may be indicated based on history and physical examination.
- Immunologic testing is generally not warranted.
  - Abnormalities are rare and opportunistic infections do not occur in CFS.

IMAGING

- Chest and sinus radiography
  - Used to eliminate other causes of symptoms
- Magnetic resonance imaging
  - In some patients with CFS, increased white matter on T2-weighted scans is suggestive of
    - Possible infiltration of the perivascular spaces
    - Focal demyelination
    - Disease of the small blood vessels of the cerebral white matter
  - The significance of these finding is uncertain.

DIAGNOSTIC PROCEDURES

- Head-upright or tilt table testing
  - Used to assess the role of postural orthostatic tachycardia syndrome (POTS)
  - Appropriate for the subset of patients in whom dizziness is a significant symptom

TREATMENT APPROACH

- A coordinated approach minimizes doctor shopping, unnecessary testing, and unconventional therapies.
  - Provide counseling and symptomatic relief for depression, sleep disorders, and musculoskeletal pains.
  - Offer emotional support with involvement of a social worker, psychologist, or psychiatrist as needed.
  - Identify and eliminate secondary gain from continuing to contribute to the illness.
  - Devise programs with the patient to increase school (or work) attendance and exercise capability gradually.
- No specific therapy for CFS has been proven to be effective.

SPECIFIC TREATMENTS

- Confirm the diagnosis of CFS and acknowledge the symptoms as real.
- Explain and explore the potential relationship to psychological symptoms.
  - Use team approach and coordinate services.
- Stress-coping skills.
  - Modify lifestyle.
  - Develop a realistic schedule.
    - Work with school on gradual return to classes, home tutoring, and neuropsychometric testing.
  - Develop a graduated exercise program.
- Cognitive-behavioral approaches.
  - Pay attention to sleep patterns and nutrition.
  - Increase activity gradually.
- Psychological support.
  - Individual and family therapy.
  - Decrease secondary gain.
- Symptom-based management.
  - In documented POTS, dietary (eg, increased salt intake) or pharmacologic management (or both) may be beneficial.
    - Medications, such as fludrocortisone, propranolol, or midodrine.
    - Therapy for neurally mediated hypotension has been only of partial benefit, even in adolescents whose tilt table tests are outside reference range.
  - Immunoglobulin injections have been reported to be beneficial in a study of patients with CFS.
    - Subsequent studies failed to confirm this observation.

WHEN TO REFER

- To resolve issues relating to possibility of ongoing infection or inflammation that may be causing the patient's symptoms.
- Given the often extensive and varied complaints of patients with CFS, multiple specialists may become involved and multiple laboratory tests may be ordered. A coordinated team approach to avoid redundant or unnecessary testing can be beneficial.
- To provide an increased level of supportive care or counseling than can be provided in the office setting, especially if the individual is not able to attend school or participate in normal activities.

FOLLOW-UP

- Periodic physical examinations.
  - Monitor for other possible conditions.
  - Monitor physical symptoms and psychological issues.
- Provide ongoing guidance and continued reassurance.
- Be aware of untested fad therapies that the patient may investigate.
  - Megavitamin treatment
  - Immune modifiers (eg, Ampligen, thymic extract, interleukin 2)
  - Magnesium sulfate
  - Liver extract injections
  - Anti-*Candida* diets
  - Colonic irrigation
  - Removal of dental fillings

PROGNOSIS

- Most patients report improvement or resolution of symptoms over 2–3 years.
- Few patients report progressive symptoms, although symptoms may wax and wane.
- With better definition of the nature of CFS, additional therapeutic approaches may become available.

Coagulation Disorders

DEFINITION

- Hemophilia A (deficiency of factor VIII, or antihemophilic factor) and hemophilia B (deficiency of factor IX, or Christmas factor) are X-linked recessive disorders with similar clinical manifestations.
- Von Willebrand disease (VWD) is the most common hereditary coagulation disorder.

SIGNS AND SYMPTOMS

- Hemophilia A and B
  - Hemarthrosis
    - Recurrent bleeding into joints is the hallmark of severe hemophilia.
    - Knees, ankles, and elbows are commonly involved, but bleeding can occur in any joint.
    - Common to see one particular target joint where recurrent episodes and chronic changes are most likely.
    - Synovial thickening and vascular friability may result in increased susceptibility to bleeding.
    - Synovitis accompanied by chronic effusion may progress to joint destruction (hemophilic arthropathy) and severe disability.
  - Soft tissue bleeding
    - Superficial hematomas.
    - Bleeding into muscles or closed soft tissue compartments may result in nerve or vascular compression, muscle fibrosis, and contractures.
      - Minimal swelling may make diagnosis difficult.
    - Bleeding into the iliopsoas muscle may cause femoral nerve damage and must be considered with pain in the lower abdomen, hip, or groin.
      - Limping and flexion of the hip are often the only positive findings.
      - Patients can lose enough blood to compromise perfusion and induce shock before obvious symptoms develop.
      - Index of suspicion for iliopsoas bleeding must be high and the threshold for therapy and imaging low in the setting of vague abdominal pain.
    - Calf bleeding may result in peroneal nerve damage.
    - Bleeding into the thigh may cause large accumulation of blood without much external change and may result in significant anemia.
  - Life-threatening bleeding
    - Intracranial bleeding after trauma or spontaneously.
      - All but the most minor head injuries must be considered significant and treated promptly.
    - Consider airway compromise a potential threat with any hematoma of the neck, submental or sublingual areas, and retropharyngeal or parapharyngeal regions.
    - Severe sore throat or dysphagia suggests bleeding and should be evaluated and treated immediately.
    - Retroperitoneal bleeding may be massive before detection and must be considered when abdominal or groin pain is present.
  - Mouth bleeding
    - Areas of frequent trauma in young children include
      - Lip
      - Tongue
      - Frenulum
    - Epistaxis is not common in patients with hemophilia, but blood loss can be significant and result in iron deficiency.
  - Hematuria
    - Evaluate with noninvasive procedures to rule out intrinsic renal disease.
- VWD
  - Manifestations
    - Bleeding after surgery and trauma
    - Mucosal bleeding (most frequently as epistaxis)
    - Menorrhagia
    - Gastrointestinal bleeding (less common)
    - Hemarthrosis and deep hematomas may be seen in severe (type 3) VWD.
- Other bleeding disorders (**Table 1**)
  - Factor XI deficiency, afibrinogenemia, and dysfibrinogenemia can be associated with bleeding in their heterozygous and homozygous forms.

DIFFERENTIAL DIAGNOSIS

- VWD.
  - A major differential diagnosis, although much rarer, is one of the disorders of platelet function.
- Differentiate normal "childhood-pattern bruising" from pathologic bruising.

Table 1. Rare Inherited Coagulation Defects

Coagulation Defect	Incidence	Inheritance	Severity	Treatment
Factor VI	Rare, 5% in Ashkenazi Jews	Autosomal recessive (*4q32q3*)	Mild to severe	FFP Half-life 52 h Factor XI concentrate available in Europe
Prothrombin (factor II)	1:2,000,000	Autosomal recessive (*11p11–q12*)	Mild to moderate	Prothrombin complex Half-life 60 h
Factor V	1:1,000,000	Autosomal recessive (*1q21–q25*)	Mild to moderate	FFP Half-life 15 h
Factor VII	1:500,000; 1:1,500 mild	Autosomal recessive (*13q34*)	Mild to severe	Recombinant Half-life 5 h
Factor X	1:500,000	Autosomal recessive (*13q34*)	Mild to severe	FFP Half-life 40 h
Factor XII	Rare	Autosomal recessive (*5q33*)	No bleeding	No treatment
Prekallikrein	Rare	Autosomal recessive (*4q35*)	No bleeding	No treatment
High molecular weight kininogen	Rare	Autosomal recessive (*3q27*)	No bleeding	No treatment
Factor XIII	1:1,000,000	A subunit: *6p24–p25* B subunit: *1q31–q32*	Moderate to severe	Factor XIII concentrate Cryoprecipitate Half-life 150 h
Afibrinogenemia	Rare	Autosomal dominant (various mutations at *4q31*)	Variable	Cryoprecipitate RiaSTAP (fibrinogen concentrate)
Dysfibrinogenemia	Rare	Autosomal dominant (various mutations at *4q31*)	Variable	Cryoprecipitate Anticoagulation if thrombosis

Table 1 (*continued*)

Coagulation Defect	Incidence	Inheritance	Severity	Treatment
Hypofibrinogenemia	Rare	Autosomal dominant (various mutations at *4q31*)	Variable	Cryoprecipitate RiaSTAP (fibrinogen concentrate)
Combined F5 and F8	Rare	Autosomal recessive (*18q21*, *2p21*)	Moderate to severe	Recombinant factor VIII Assess response to DDAVP FFP
Combined deficiency of vitamin K–dependent clotting factors	Rare	Autosomal recessive (*16q12–q21*, *2p12*)	Variable	FFP

Abbreviations: DDAVP, trademark for preparations of desmopressin; FFP, fresh frozen plasma.

- Pattern of childhood bruising is often related to the degree of mobility.
  - Bruising in babies unable to walk is uncommon (<1%).
  - Evaluate such patients for coagulation disorders or non-accidental trauma.
- Bleeding disorders are clinically indistinguishable from abusive bruising in immobile young children.

DIAGNOSTIC APPROACH

- Detailed assessment of bleeding history and a physical examination guide laboratory studies.
- Evaluate all immobile young children with bruising for a bleeding disorder and non-accidental trauma simultaneously.
- Detailed history should also specify
  - Site of bleeding
  - Age at which bleeding was first noticed
  - Severity
  - Triggers for bleeding
  - Medications
  - Hemostatic challenges (eg, bleeding after surgeries and dental procedures)
  - Family history
    - History of a similar bleeding pattern in other male family members may suggest hemophilia.
    - Absence of a family history should not deter from further investigations because spontaneous mutations are seen in 30%–40% of patients with hemophilia.
    - Type 1 VWD has an autosomal-dominant pattern of inheritance but may have variable expression in affected members.
- Recent bleeding assessment questionnaires/tools are being validated for use in children.

LABORATORY FINDINGS

- Usual screening tests.
- Complete blood cell count with review of the morphology of the peripheral blood.
- Activated partial thromboplastin time (aPTT).
- Prothrombin time (PT).
- Falsely prolonged clotting times may result from
  - Insufficient amount of blood in the specimen tube
  - Difficulty accessing the vein with release of tissue factor and consumption of coagulation factors
  - Contamination with heparin or intravenous (IV) fluids
- The tests are sensitive to clotting factor levels <30%–40% of normal.
- If the PT or aPTT is prolonged, repeating tests or referral to a specialist may be indicated based on presence and severity of symptoms.

- PT
  - Measures the activities of factors I (fibrinogen), II (prothrombin), V, VII, and X.
  - Prolongation beyond reference range is often not seen until the functional level for one of these factors is <30% or fibrinogen level is <100 mg/dL.
  - Isolated prolongation of PT may reflect factor VII deficiency.
  - Although rare, PT can also be prolonged by a circulating inhibitor or abnormal fibrinogen molecules or D-dimer fragments in the circulation.
  - PT is useful for monitoring the effect of coumarin-type anticoagulants.
    - When monitoring a patient on warfarin, consider differences in thromboplastin sensitivities.
      - This has led to development of a standardized method of expressing the prolongation as an international normalized ratio (PT-INR).
      - INR = (patient's PT/control PT)$^{\text{International Sensitivity Index (ISI)}}$
      - ISI should be determined for each thromboplastin reagent and instrument.
- aPTT
  - Measures factors I (fibrinogen), II (prothrombin), V, VIII, IX, X, XI, XII, prekallikrein, and high-molecular-weight kininogen.
    - Deficiency of any of the latter 3 factors can result in a markedly prolonged aPTT in the absence of clinically significant bleeding.
  - Isolated prolongation of the aPTT in a patient with clinical bleeding is likely to result from a deficiency of factor VIII, IX, or XI.
  - Sensitivity and reproducibility of the aPTT depend on the specific reagents used (particularly the activator in the partial thromboplastin reagent).
  - Laboratory should establish reference range for each new lot of reagent and each new method of clot detection.
  - Reference range.
    - About 26–35 seconds for children and adults
    - 30–54 seconds in term newborns
    - Often even longer in preterm newborns
  - Somewhat less sensitive than PT to the deficiency of vitamin K–dependent factors.
  - More sensitive to the presence of circulating anticoagulants and heparin.
  - Can detect circulating anticoagulants (eg, lupus anticoagulants).
  - Routinely used to monitor standard heparin therapy.
- Thrombin time (TT)
  - Measures
    - Thrombin-induced conversion of fibrinogen to fibrin
    - Amount and clotting function of fibrinogen
  - Prolonged in the presence of heparin or circulating fibrin degradation products.
  - Extremely prolonged TT usually indicates a heparin effect.
  - The snake venom protease, reptilase, clots fibrinogen in the presence of heparin and can be used to identify heparin as the cause of the prolonged TT.
    - In the presence of heparin, the TT is prolonged, while the reptilase time is normal.
  - Heparin activity can also be tested by its anti–factor Xa activity or with the use of commercial heparinase.
  - Sensitivity of TT can be increased by dilution of the thrombin to give a control thrombin clotting time of 16 to 18 seconds.
  - Normal values differ among laboratories and between instruments and reagents.
    - Compare resulting values with the reference range for that laboratory.
  - In children, normal values for coagulation and anticoagulant proteins differ with age.
    - Compare values obtained with reference values for the age of the patient.
- Bleeding time
  - Once considered a useful screening test for VWD.
  - Difficult to standardize.
  - Poor sensitivity and specificity.
  - High interobserver and intra-observer variations.
  - Has been replaced in many centers by the platelet function analyzer (PFA-100), a commercially available instrument.
    - Quantitative
    - Simple
    - Rapid
    - Reproducible
    - Measures, under high shear stress, the time taken for a platelet plug to occlude a microscopic aperture in a membrane coated with platelet agonists
    - Lacks sensitivity for mild VWD and platelet disorders
  - If the history is suggestive, level analysis or formal platelet aggregation tests may be appropriate.

- Hemophilia A and B
  - Laboratory studies often show a prolonged aPTT with a normal PT and normal tests for platelet function.
  - Specific factor assays for factors VIII and IX identify the deficiency.
  - Severe hemophilia.
    - 80% of cases of hemophilia A and 60% of hemophilia B
    - Defined by a factor VIII or IX level <1%
  - Mild disease: factor VIII or IX levels between 5% and 40%.
  - Moderate disease: levels between 1% and 5%.
  - Accurately diagnosing disease severity is important because spontaneous bleeding is common in severe hemophilia; those with moderate to mild hemophilia have trauma-induced bleeding.
  - In most families, diagnosing hemophilia prenatally is possible by chorionic villus biopsy or amniocentesis.
  - Factor VIII and factor IX genes have both been cloned.
  - Many different mutations have been identified in both conditions.
- VWD
  - Bleeding time and PFA-100 test are fairly sensitive, but nonspecific, and are prolonged in most patients.
  - Most cases are associated with mildly decreased levels of factor VIII.
  - aPTT may be normal if factor VIII is >30%–40%.
  - All studies may be variable, from patient to patient and from time to time.
  - Even if test results are normal, repeat if the index of suspicion is high.
  - VWF level varies with blood type and with several environmental factors.
  - VWF levels of 35%–50% may exist in patients with VWD and normal individuals with blood type O.
- Other bleeding disorders
  - Factor XIII deficiency cannot be detected with the usual screening tests.
  - Normal screening workup in a patient with a significant bleeding history should be followed with a clot solubility test.
  - The contact factors prekallikrein, high-molecular-weight kininogen, and factor XII are necessary to initiate clotting in vitro.
  - Their absence results in a markedly prolonged aPTT but is not associated with clinical bleeding.

IMAGING

- Soft tissue bleeding
  - Sonography or computed tomography (CT)
- Life-threatening bleeding
  - Consider appropriate imaging based on age of the child.
    - Newborn: ultrasound.
    - Older children: CT scan of the head may be more appropriate.
  - Treat with factor replacement before obtaining imaging studies because delay may have an adverse outcome.
  - In retroperitoneal bleeding, CT or magnetic resonance imaging may be helpful.

CLASSIFICATION

- VWD
  - Type 1
    - All components are similarly reduced and the multimer pattern is normal.
  - Type 2
    - Results from qualitative defects in VWF
    - Can include decrease or absence of the larger multimers
    - Type 2B
      - Increased binding to platelets
    - Type 2N
      - Results from impaired binding of factor VIII and resulting low factor VIII levels.
      - Can be misdiagnosed as mild to moderate hemophilia A.
      - Consider in the differential diagnosis of mild or moderate hemophilia A, particularly in the absence of family history.
      - Often diagnosed after poor response to factor VIII replacement or when an affected female family member is found to have low factor VIII activity.
  - Type 3
    - Severe homozygous deficiency with very low or absent levels of all components

TREATMENT APPROACH

- Hemophilia
  - Ideal management is in a comprehensive hemophilia treatment center that provides multiple services.
    - Medical
    - Orthopedic
    - Physical rehabilitation
    - Dental
    - Psychosocial

- All elective surgical procedures must be performed in a center with
  - Experienced personnel
  - Immediate availability of blood clotting factor assays
  - Ready supply of clotting concentrates
- Evaluate factor inhibitors before elective procedures.
- Avoid
  - Nerve blocks
  - Intramuscular injections
  - Arterial blood draws
  - Antiplatelet medications, such as aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs)
- Always give factor replacement as promptly as possible when bleeding is suspected before performing imaging or other diagnostic studies.
- Give a patient with a severe injury or life-threatening bleeding an immediate dose of the appropriate clotting factor to raise its level to 100%, and then transfer to a hemophilia center.
- Treat any significant injury promptly, even without apparent evidence of active bleeding, given that bleeding is often delayed.
- Small, superficial laceration.
  - If not bleeding or in need of cleaning or sutures, manage with a simple pressure dressing.
  - If bleeding occurs or suturing is required, immediately administer appropriate clotting factor.
  - Do not apply casts unless factor has been administered beforehand and is continued for several days afterward.
  - Watch the involved area closely for evidence of nerve or vascular compression.
- Provide factor replacement before all surgical procedures, arterial punctures, and lumbar punctures.
- Pain.
  - Manage with acetaminophen whenever possible.
  - Provide codeine and other oral narcotics if necessary.
  - Non-acetylated salicylates (eg, choline magnesium trisalicylate [Trilisate]) can be used.
  - NSAIDs, such as ibuprofen, can be given cautiously if the patient is not also receiving zidovudine.
  - Cyclooxygenase-2 inhibitors.
    - Showed early promise as analgesic agents for patients with hemophilia.
    - Cardiovascular toxicity that led to the withdrawal of rofecoxib from the market suggests that these drugs should not be used routinely until more is known.
  - Ketorolac may be more effective for treatment of musculoskeletal and joint pain.
  - Treat bleeding episodes as early as possible to limit severe pain and minimize need for narcotics.

SPECIFIC TREATMENTS

Hemophilia A and B

- See **Table 2** for factor replacement details.
- Whole plasma.
  - Because of the large volume and protein load that accompany its use
    - Can increase factor VIII levels to only 40%
    - Can increase factor IX levels to 20%
- The safety of current concentrates makes them the preferred mode of treatment in most situations.
- Recombinant factors VIII and IX are available and effective and appear to be free of viral contamination.
  - Some studies have indicated an increased incidence of inhibitor development with these products, although others have not.
- Factor IX is available in the form of prothrombin complex, as well as in purified and recombinant forms.
- Mild bleeding requiring a single treatment can be managed with the complex.
  - This approach has a risk of thrombosis or disseminated intravascular coagulation (DIC) from activated factors, particularly in patients with liver disease.
- The Medical and Scientific Advisory Committee of the National Hemophilia Foundation recommends the use of recombinant factor products when available because of decreased risk for viral infections.
- Generally, treat patients with only one brand of factor product.
  - Switching products may be associated with inhibitor development.
- Desired levels of factor VIII or IX for managing different clinical problems are shown in **Table 3**.
- Continuous infusion can be used for patients who are undergoing surgery or who are bleeding extensively.

Table 2. Products Available for Treatment of Coagulation Disorders

Product	Content	Dose, Concentration, Size of Units	Indications, Comments
Fresh frozen plasma	Whole plasma	5–15 mL/kg; 1 U of each of the coagulation factors/mL; 220 or 600 mL/bag	Multiple factor deficiency; DIC; reversal of Coumadin effect; HUS or TTP; unknown coagulation defect; when no specific concentrate exists; not virus inactivated
Cryoprecipitate	Factor VIII, factor XIII, fibrinogen, fibronectin	1 U/kg raises factor VIII 2%; 75–100 U factor VIII and WF/bag; volume ~20 mL; not assayed.	Factor XIII deficiency, hypofibrinogenemia; derived from single-donor units; not virus inactivated
Factor VIII	Factor VIII	1 U/kg raises factor VIII 2%; pre-assayed; up to 100 U/mL.	Hemophilia A; made by various methods, with different levels of purification; recombinant product available; virus inactivated[a]
Humate P	Factor VIII, VWF	Pre-assayed; factor VIII 20-40 U/mL; 50–100 U/mL	Severe VWD; mild to moderate VWD if DDAVP ineffective or inadequate; virus inactivated[a]
Factor IX	Factor IX	1 U/kg (1.2–1.4 U/kg of recombinant) raises factor IX 1%; pre-assayed; up to 100 U/mL.	Hemophilia B; recombinant product available; virus inactivated[a]
Prothrombin complex	Factor II, VII, IX, X	Pre-assayed for factor IX; content of other factors varies among products.	Hemophilia B when purified factor IX cannot be used; mild bleeding in hemophilia A with inhibitor; congenital deficiency of factor II or X; danger of thrombosis (including MI and DIC) in presence of liver disease, prolonged use; virus inactivated[a]
Activated prothrombin complex	Factor II, VII, IX, X; factor VIII bypassing activity	Pre-assayed for ability to shorten aPTT of plasma with high-titer factor VIII inhibitor	Hemophilia A or B with inhibitor; cannot evaluate response by measuring factor VIII activity; risk for DIC and thrombosis
	Recombinant factor VIIa	Pre-assayed	Hemophilia A or B with inhibitor; factor VII deficiency; risk for thrombosis

Abbreviations: aPTT, activated partial thromboplastin time; DDAVP, trademark for preparations of desmopressin; DIC, disseminated intravascular coagulation; HUS, hemolytic uremic syndrome; MI, myocardial infarction; TTP, thrombotic thrombocytopenic purpura; VWD, von Willebrand disease; VWF, von Willebrand factor.

[a] Virus attenuation processes may not inactivate parvovirus, hepatitis A, and possibly other viruses.

Table 3. Treatment of Bleeding Episodes in Hemophilia

Type of Bleeding	Desired Level of Factor VIII or IX	Duration of Treatment	Ancillary Treatment
Hematoma, simple	20%–40%	Usually once	–
Hemarthrosis, mild muscle hematoma	30%–40%	Once, as soon as symptoms begin; if severe, repeat daily until better clinically.	Non–weight bearing and rest; gradual initiation of passive physical therapy; pain control
Severe muscle hematoma	50%–100%	3–7 d	Check hemoglobin because large hematomas may cause anemia; non–weight bearing and rest; gradual initiation of passive physical therapy; pain control.
Mouth bleeding, epistaxis, dental extractions	80%–100%	Once	Start EACA 75–100 mg/kg every 6 h or tranexamic acid 25 mg/kg every 6–8 h by mouth for 3–7 d (until clot is gone).
Gastrointestinal bleeding	100%	3–7 d	EACA or tranexamic acid
Hematuria	Factor may not be needed.	3–7 d	Bed rest; hydration; do not use EACA.
Life-threatening, central nervous system, airway obstruction, retroperitoneal	100%; do not allow drop <50%.	7–14 d	Monitor factor and inhibitor levels.
Surgery	100%; do not allow drop <50%.	7–14 d	Preoperative inhibitor testing; monitor levels.
Prophylaxis	20–40 U/kg	3 times per week for factor VIII 2 times per week for factor IX	Demonstrated to improve joint outcomes

Abbreviation: EACA, e-aminocaproic acid.

A total of 1 U/kg of factor VIII increases plasma level by 2%; biologic half-life = 10–12 hours. A total of 1 U/kg of factor IX increases level by 1%; 1 U/kg of recombinant factor IX increases level by 0.8%; biologic half-life = 20–24 hours. Slightly lower levels of factor IX than of factor VIII are effective.

Initial dose = 50 U/kg of factor VIII and 80–100 U/kg of factor IX; repeat one-half the factor VIII dose in 8–12 hours and one-half the factor IX dose in 12–24 hours, or provide a continuous infusion of 3–4 U/kg/h of either factor VIII or factor IX after initial bolus dose.

- Health care maintenance.
  - Routine immunizations must include hepatitis B and hepatitis A vaccines.
    - Should be given subcutaneously, if possible, with a 25-gauge needle.
      - Intramuscular injections are controversial but are probably safe when a small needle (≤23 gauge) is used and pressure is held for 1–2 minutes.
        - ▶ Can also be scheduled after routine factor replacement in patients on prophylaxis
      - Maintain pressure for 5–10 minutes.
      - Effectiveness of hepatitis A vaccine administered subcutaneously is good, but this is less clear for other vaccines.
  - Routine dental evaluation, prophylaxis, and hygiene should begin by 3 years of age.
- Home management.
  - Parents can be taught to administer treatment to children as young as 3 years.
  - 9- or 10-year-olds can be taught to self-administer factor concentrates.
    - Allows for much earlier treatment of bleeding episodes
    - Provides the satisfaction of self-sufficiency
    - Prevents frustrations of having to get to a treatment center or emergency department
  - Indwelling venous access devices
    - Have simplified home and in-hospital management
    - Possibly complicated by infections and thrombosis
  - Home IV therapy is also convenient for administration of prophylaxis or immune tolerance induction.
  - Caregivers should receive adequate education and training and perform infusions under the supervision of medical staff until proficient.
- Mild hemophilia.
  - More likely than those with severe disease to receive inadequate treatment of bleeding episodes.
  - Significant injuries require management similar to that in patients with severe disease, although smaller doses of factor concentrates may be sufficient.
  - Desmopressin (DDAVP).
    - Results in release of factor VIII from the endothelial cells and almost a 3-fold increase of the level.
    - May be effective if the baseline factor VIII level is >5%, depending on the level desired.
    - Prevent overhydration because water retention and hyponatremia may occur with DDAVP therapy, particularly in young children and with repeated doses.
    - Stimate, a concentrated intranasal preparation, is available and has been used in children ≥6 years.
    - Perform stimulation test in each patient before IV or intranasal therapies are used for the first time.
    - Response to DDAVP often correlates with the causal genetic mutation and patient age.
    - Response has been tested in infants and children ≥11 months, but there is no consensus on the optimal age for testing DDAVP response.
    - Most centers wait until patients are ≥3 years before a DDAVP challenge because of concerns of hyponatremia and possible lack of response.
    - Ineffective in factor IX deficiency.
- Prophylaxis with factor concentrate administered several times per week is optimal in severe hemophilia.
  - Prevents hemarthrosis and joint damage
  - Normalizes patients' lives
  - More expensive than episodic treatment for bleeding, but considerable costs saved by prevention of future orthopedic complications
  - Psychological benefits
- Inhibitors.
  - ~30% of patients with severe hemophilia A and 3% with hemophilia B develop antibodies that inhibit factor VIII or factor IX activity, usually early in treatment.
    - Many are present in low titer and may subsequently disappear.
  - Inhibitor antibodies are more common in patients with
    - Severe hemophilia
    - Large gene deletions
    - Family history of inhibitors
  - Most inhibitor antibodies develop before the 20th infusion of factor products but can develop at any time.
  - Suspect an inhibitor if the response to appropriate therapy is inadequate and in all patients before all elective surgery.
  - A Bethesda inhibitor assay will determine the presence and strength of an inhibitor.

- Management may include
  - Large doses of factor VIII or factors that bypass factor VIII in the coagulation cascade
    - Prothrombin complex, activated prothrombin complex, recombinant factor VIIa
  - Use of porcine factor VIII
- Induction of immune tolerance by continuous exposure to high doses of factor over many weeks to months, with or without concomitant immunosuppression, controls the inhibitor in most cases.
- Patients with hemophilia B with inhibitors may develop anaphylaxis or nephrotic syndrome when given factor IX.
- Management is much more difficult than for hemophilia A, but recombinant factor VIIa has been effective.
- Because of the incidence of life-threatening anaphylactic reactions in hemophilia B, the first 20–30 factor infusions should be administered in a facility capable of treating anaphylaxis.

■ Gene therapy.
- Results of gene transfer of factor VIII and factor IX genes in animal models and clinical trials have been disappointing.
- Concerns about the possibility of inducing malignancy or liver disease remain.

■ Hemarthrosis.
- Must be treated as soon as pain, tingling, or limping begins.
  - Watchful waiting is not appropriate for the child who has moderate or severe hemophilia.
- Continue prompt replacement of factor VIII or factor IX until signs of joint swelling resolve.
- Primary prophylaxis before the first bleed is an effective therapy for reducing joint bleed-related morbidity.
- After a joint bleed occurs in a patient with hemophilia, factor prophylaxis 2–3 times a week should be strongly encouraged.
- The difficulties of IV access may interfere with early prophylaxis.
  - Consider central venous access devices.
- Synovectomy by open, arthroscopic, or radionuclide approaches may be effective if medical management fails.
- Radio-synovectomy is a simpler procedure, requiring less factor replacement and physical therapy.
  - Although performed in young children with good joint outcomes, some concern exists about the possibility of inducing malignancy.

■ Mouth bleeding.
- Use factor replacement plus aminocaproic acid or tranexamic acid to prevent fibrinolysis.
- Use these drugs cautiously in patients receiving prothrombin complex or any activated coagulation factors.
  - The combination can lead to thrombosis or DIC.

■ Hematuria.
- Usually resolves spontaneously with or without factor replacement.
  - Bed rest and hydration are often suggested.
- Avoid fibrinolytic agents and factor replacement unless bleeding is known to originate in the lower urinary tract.
  - Can result in obstruction of the renal pelvis by clot formation
- Steroid role is controversial, but these drugs are probably not beneficial.

■ The most difficult part of managing the child who has hemophilia is to balance appropriate caution while allowing development of independence.
- Family education
- Support groups
- Close monitoring for psychosocial issues
- Obtaining and maintaining insurance

VWD

■ DDAVP
- Effective for most patients with type 1 VWD.
  - This approach can be used for most bleeding episodes.
- Most patients with type 2A and all with type 3 VWD do not respond.
- Contraindicated in type 2B VWD because it may cause platelet aggregation and DIC.
- A trial dose should be used to assess response, with levels tested before administration and ≤4 hours after dosing.
  - Some patients respond poorly.
  - Allows detection of variants with rapid clearance of endogenous VWF.
- Patients who have severe bleeding or those not responsive to DDAVP should be treated with a concentrate that contains factor VIII and VWF (Humate-P or Wilate).

- Fresh frozen plasma or cryoprecipitate can be used, but neither is suggested because of the possibility of viral contamination.
- Mild epistaxis can often be controlled with e-aminocaproic acid or tranexamic acid.
  - These agents should also be used as adjunctive therapy for mucosal bleeding other than hematuria.

Other Bleeding Disorders

- See **Table 3** for specific recommendations.
- All can be treated with fresh frozen plasma.
- Concentrates are preferable for treating factor VII deficiency because of its short half-life, as well as other deficiencies when available because they are virus depleted.
- Recombinant factor VIIa is commercially available.
- Prothrombin complex products also contain factor VII, as well as factors II and X, but the content of each factor varies in different lots.
- These products contain activated coagulation factors that may induce thrombosis or DIC.
  - They must be used cautiously, particularly in patients with liver disease.
  - Fibrinogen and factor XIII are concentrated in cryoprecipitate.
  - Factor XIII concentrate may be available for compassionate use.
  - Fresh frozen plasma can be used for patients with factor V or XI deficiency or in an emergency for patients who are bleeding but whose deficiency has not yet been identified.
  - Factor XI concentrates are available in some European countries but not yet in the United States.

WHEN TO ADMIT

- Significant trauma.
- Bleeding in a potentially life-threatening area.
- Severe abdominal pain.
- Any surgical procedure must be performed.

WHEN TO REFER

- All children with hemophilia should be seen at least once a year at a comprehensive hemophilia center if possible.
- All elective surgery should be performed at a hemophilia center.
- All patients with significant trauma or potentially life-threatening bleeding should be given an initial loading dose of factor (to 100%) and transferred to a hemophilia center.
- All patients with inhibitors should be managed at a hemophilia center.
- Children with VWD should have an initial evaluation by a specialized coagulation laboratory.
- All newly diagnosed patients with a bleeding disorder should be referred to a geneticist for consultation on implications and screening (if necessary) in other family members.

COMPLICATIONS

- AIDS and other viral infections
  - Most patients who had severe hemophilia in the United States in the late 1970s and early 1980s became infected with HIV.
  - Treatment of hemophilia with clotting factor concentrates from large donor pools in the era before the virus was identified resulted in massive exposure to HIV.
  - Chronic liver disease has also been a major problem, most often caused by hepatitis C and sometimes by hepatitis B virus infection.
  - Concerns about HIV and hepatitis B and C have been eliminated by donor testing and improved production processes.
  - Hepatitis A and parvovirus B19 infections may still occur with plasma products.
  - The increasing availability and use of recombinant factors may eliminate the problem of viral infections.

PREVENTION

- Future pregnancies
  - Because these are inherited conditions, screening other family members may be appropriate.
  - Referral to a geneticist specializing in bleeding disorders may be appropriate, especially to identify and counsel carriers.

DEFINITION

- Inconsolable crying that
  - Occurs for >3 hours per day *and*
  - Occurs >3 days per week *and*
  - Follows the typical crying curve, starting in the second week, peaking at 6 weeks, and often resolving by 4 months

SIGNS AND SYMPTOMS

- Colic presents as bouts of crying, fussing, or irritability that may develop into agonized screaming.
- The baby may draw up his or her knees against the abdomen, as if in pain.
- Symptoms follow the typical crying curve.
  - Crying bouts begin in the second week.
  - Crying peaks at 6 weeks.
  - Crying usually resolves by 4 months of age.
  - Crying bouts are more common in the evening hours.
- It has been suggested that colic represents the upper end of the continuum of typical crying.
- Babies seem inconsolable during these crying periods.
  - Feeding, diaper changes, and soothing techniques are not effective in halting the crying.

DIFFERENTIAL DIAGNOSIS

- Crying in the newborn can be a sign of any number of disease processes; thus, they must be excluded before colic can be diagnosed.
- Gastroesophageal reflux disease.
  - Presents with episodes of fussiness
  - Often accompanied by emesis, which occurs soon after feeding
- Milk protein intolerance.
  - Crying accompanied by diarrhea or hematochezia
- If the mother used alcohol or other drugs during pregnancy, the baby may be excessively fussy.
- All of the following conditions typically present with persistent, rather than paroxysmal, symptoms:
  - Corneal abrasion
  - Hair tourniquet
  - Acute abdominal processes that constitute medical emergencies and symptoms, including anorexia or vomiting
    - Volvulus
    - Intussusception
    - Incarcerated hernia
  - Infectious processes, usually accompanied by fever
    - Otitis media
    - Urinary tract infection
    - Meningitis
  - Inflicted injuries
    - Fractures
    - Intracranial bleeding

DIAGNOSTIC APPROACH

- A complete history is essential.
  - Parents may state that the baby is fussy and has excessive gas.
  - They may be concerned that the baby is in pain.
  - Ask
    - When did symptoms begin?
    - How often do they occur?
    - During what part of the day do the symptoms occur?
    - How long do symptoms last?
    - What have you done to try to ameliorate the symptoms?
    - What interventions, if any, are effective?
  - Obtain a history of the pregnancy.
    - Determine whether there was any maternal alcohol or drug use.
    - Determine whether there were any infections during pregnancy.
  - Family history.
    - Metabolic or allergic disorders
    - Sibling with colic
  - Social history.
    - Assess parental anxiety about real or perceived health concerns.
    - Ask who in the family is responsible for caregiving.
    - Ask what types of support for caregiving are available to the family.
  - Review of systems.
    - Inquire about organic signs and symptoms of irritability, including
      - Fever
      - Lethargy
      - Vomiting
      - Diarrhea
      - Hematochezia
  - Review feeding techniques and history.
    - For formula-fed babies
      - Ensure that formula is being prepared correctly.
      - Assess whether the baby is being overfed or underfed.

- For breastfed babies
  - Assess the mother's supply of milk.
  - Review how often and for how long the baby is fed.
- Physical examination.
  - Generally serves to exclude pathologic abnormalities.
  - In most cases, physical examination will be normal.
  - Acute abdominal processes, otitis media, and hair tourniquet can all be excluded by physical examination.
  - Determine weight, length, and head circumference and plot on a growth chart.
    - Poor growth suggests inadequate nutrition or other organic causes for crying.
    - Increasing head circumference suggests hydrocephalus or abuse.

LABORATORY FINDINGS

- Laboratory testing is seldom indicated.
  - Should be reserved for cases in which an organic cause is suspected
- Unnecessary laboratory testing should be avoided because it may convey to the parents the message that the baby is ill.

TREATMENT APPROACH

- Management primarily involves parental education and support.
  - Teach the parents that the baby is not sick.
  - Excessive crying is not harmful.
    - Use the baby's normal growth and results from the physical examination to reinforce this.
  - Reassure parents about their abilities as caregivers.
  - Emphasize that they are not to blame for the baby's symptoms.
- Acknowledge the parents' frustration.
  - Inform them that the office will provide support.

SPECIFIC TREATMENTS

- Teach parents to respond to the baby's fussiness with a predictable set of responses.
  - Having a plan to use during fussy periods can be reassuring.
- First, make sure the baby is not hungry, soiled, or tired.
  - Soothe the baby by encouraging
    - Nonnutritive sucking
    - Swaddling
    - Gentle rocking or swinging
- It is acceptable to allow the baby to cry for a short period.
  - Allows the parents to regroup
  - Provides the baby with some time to blow off steam
- Educate parents about crying.
  - Most parents are surprised to learn how much healthy babies cry.
  - Highlight the differences among healthy babies.
    - Some babies are just naturally fussier.
  - The mnemonic PURPLE, from the Period of PURPLE Crying program (aimed at preventing abusive head trauma), can be used to remind parents of the pattern of normal, healthy crying that can cause stress and frustration in caregivers.
    - **P**eak pattern
    - **U**nexpected timing of episodes
    - **R**esistance to soothing
    - **P**ain-like face, even though baby is not in pain
    - **L**ong bouts of crying
    - **E**vening cluster of symptoms
- Support options for families, including home visiting programs.
- Parents should be encouraged to
  - Take care of themselves.
  - Get adequate rest.
  - Enlist family members or friends to take over from time to time to reduce caregiver stress.
- Few medical interventions are helpful for colic.
  - If indicated by history, changing to hypoallergenic formula may be considered.
  - For breastfeeding mothers, consider an elimination diet.
  - If symptoms suggest reflux, treat for gastroesophageal reflux disease.
- Pharmacologic therapies have been found to be unhelpful and possibly harmful.
  - Simethicone is not effective in symptom reduction.
  - Dicyclomine, an anticholinergic, is effective.
    - The manufacturer has advised against its use in infants <6 months.

- Herbal tea made of chamomile, vervain, licorice, fennel, and balm mint has been shown to be effective.
  - However, large volumes of fluid, 120 mL/3 times a day, may cause potential harm, such as hyponatremia or decreased milk intake.

WHEN TO ADMIT

- In the vast majority of cases, colic can be successfully managed in the outpatient setting.
- If the history is confusing or suggests more serious symptoms, admission for observation may be necessary.

WHEN TO REFER

- Referral to specialists in developmental or behavioral medicine may be useful if the parents are extremely anxious or in need of additional reassurance.
- Be alert to parents who are overwhelmed by the baby's crying and may be in danger of harming the baby.
  - In this case, referral to children's services may be necessary.

FOLLOW-UP

- Support the parents until they are comfortable managing their baby's symptoms.
- Very anxious parents may be offered a return office visit in 1 week.
- Provide support through telephone contact a few days after the initial visit.
- Excessive crying may be a stimulus for abusive head trauma (shaken baby syndrome).
  - Provide support and education to the parents and carefully assess the baby at follow-up visits.

PROGNOSIS

- Prognosis is generally good.
- Symptoms usually decrease dramatically by 4 months of age.
- The presence of colic in a baby does not necessarily predict a more difficult temperament in an older baby.
- Excessive parental anxiety and frustration may lead to later parent-child interaction problems, such as
  - Prolonged night waking
  - Overfeeding
  - Vulnerable child syndrome

DEFINITION

Congenital Defects

- Intracardiac shunting lesions
  - A defect or hole in the septum separating the 2 ventricles that allows blood to traverse from one side of the heart to the other
  - Shunting can be
    - Left side of the heart to the right
    - Right side of the heart to the left
    - Bidirectional
  - Right heart
    - Systemic veins, inferior vena cava (IVC), and superior vena cava (SVC)
    - Atrium
    - Ventricle
    - Great artery/pulmonary artery
  - Left heart
    - Pulmonary veins
    - Atrium
    - Ventricle
    - Great artery/aorta
- Left-to-right shunting lesions
  - Ventricular septal defect (VSD)
  - Atrial septal defect (ASD)
  - Patent ductus arteriosus (PDA)
  - Atrioventricular septal defect (AVSD)
  - Arteriovenous malformations
- Right-to-left shunting lesions
  - Tetralogy of Fallot
  - Eisenmenger syndrome
    - Untreated septal defects
  - Pulmonary hypertension
  - Pulmonary atresia
    - No prograde flow across the pulmonary valve
  - Isolated pulmonary valve stenosis
    - Differs from atresia by presence of prograde flow across the pulmonary valve
    - Unlike more severe forms of pulmonary atresia, coronary sinusoidal formation and right ventricular dependent coronary artery flow are absent.
  - Ebstein anomaly
  - Anomalous pulmonary venous return (PVR)
    - Total
    - Partial
  - Dextrorotation
    - Rightward transposition of the great arteries
- Left-sided obstructive lesions
  - Characterized by impedance to blood flow from the systemic ventricle (generally the left) to the body
  - Aortic stenosis
  - Coarctation of the aorta
- Complete mixing lesion/single-ventricle heart
  - Arterial oxygen saturation (SaO_2) is the same in the aorta and pulmonary artery.
    - Hypoplastic left heart syndrome (HLHS)
    - Tricuspid atresia

Acquired Heart Disease

- Infectious
  - Infectious endocarditis (IE)
    - Bacterial infection of the endocardium or endothelium of the heart
  - Myocarditis
    - Generalized inflammation of the cardiac muscular walls
  - Pericarditis
    - Inflammation of the pericardium
    - The parietal and visceral layers of the pericardium are inflamed.
- Cardiomyopathies
  - Any structural or functional abnormality of the ventricular myocardium that is not associated with congenital heart disease or diseases of the coronary arteries, cardiac valves, or pulmonary vasculature
    - Dilated cardiomyopathy (DCM)
    - Hypertrophic cardiomyopathy (HCM)
    - Restrictive cardiomyopathy (RCM)
    - Miscellaneous cardiomyopathies

SIGNS AND SYMPTOMS

Cardiac Murmur

- Functional murmur is an audible sound of blood flow through the heart or vascular system that can be auscultated in a normal heart, resulting from hyperdynamic function or a thin chest wall.
- Diastolic murmur
  - Generally indicates an abnormality
- Systolic murmur
  - May be either
    - Normal (functional)
    - Pathologic
- Regardless of the timing, location, or cause of the murmur, its frequency and pitch depend on
  - Size of the opening through which the blood flows
  - Pressure gradient across it

VSDs and ASDs

- Smaller ASDs and VSDs
  - May not be detected prenatally.
    - Usually detected by the presence of a murmur, with or without the signs of heart failure.
    - The timing of presentation depends on the size of the defect and whether the infant has fully transitioned from fetal circulation.
  - A small VSD will produce a high-pitched, holosystolic murmur that continues from the onset of ventricular systole through the closure of the atrioventricular valves (obscuring the first heart sound), to the closure of the semilunar valves.
  - In some patients, PVR never decreases after birth or decreases at a slower rate and then increases.
    - These patients will have few or no symptoms of pulmonary over-circulation.
    - As a result, they may not be brought to a physician's attention.
    - Elevated PVR produces elevated pulmonary artery pressures and commensurate pulmonary hypertension (mean pulmonary pressures >25 mm Hg at rest).
- Large VSDs
  - Produce a softer holosystolic murmur because the pressures of the 2 ventricles more closely approximate one another.
    - This murmur will be loudest at the left lower sternal border and may be best described as a mid-frequency blowing murmur.
  - A neonate with a large VSD may demonstrate poor weight gain and lethargy as PVR decreases, increasing the gradient for shunting from the left ventricle to the right.
    - If untreated, heart failure (marked pulmonary over-circulation) may ensue.
- ASD
  - Auscultation differs significantly from that of a VSD.
  - The lack of a marked pressure gradient between the 2 atria does not produce a murmur at the site of shunting.
    - Rather, the murmur of an ASD is due to excess volume traversing the pulmonary valve, commonly described as a relative pulmonary stenosis.
    - It is described as a mid-frequency systolic ejection murmur best auscultated at the upper left sternal border and will commonly radiate to the lung fields bilaterally.
  - ASD may remain asymptomatic for many years.
  - Pulmonary edema symptoms
    - Typically do not develop until the pulmonary artery blood flow has doubled in volume

PDA

- Auscultation
  - Machinery murmur (continuous, undulating).
    - Heard during systole and diastole.
    - As the ductus arteriosus begins to close, the murmur is higher in pitch.
  - Murmur is best auscultated in the left upper sternal border of the chest; it may radiate to both lung fields.
- Other signs
  - Worsening chronic lung disease
  - Poor renal perfusion
  - Hemodynamic instability
  - Intraventricular hemorrhage
  - Necrotizing enterocolitis

Tetralogy of Fallot

- Commonly detected by prenatal ultrasonography between 18 and 22 weeks' gestation
- Clinical presentation can vary greatly, depending on
  - Degree of pulmonary stenosis
  - Presence of pulmonary atresia
- Newborns
  - Cyanosis
  - Audible murmur
    - Systolic murmur may be appreciated at the left upper sternal border and is produced by the narrowing of the right-ventricular outflow tract (RVOT).
    - Grade (1–6/6) and quality (harsh or soft) depend on the degree of obstruction.
  - In the newborn with tetralogy of Fallot and pulmonary atresia
    - RVOT murmur is replaced by a flow murmur through the ductus arteriosus, the only source of pulmonary blood flow.

Eisenmenger Syndrome

- Physical examination of a patient with pulmonary hypertension caused by Eisenmenger syndrome may be virtually indistinguishable from that of a simple ASD or VSD.
  - A subtle difference may be a loud pulmonary valve component of the second heart sound.

Pulmonary Hypertension

- Idiopathic pulmonary hypertension or pulmonary hypertension secondary to bronchopulmonary dysplasia.
  - Cyanosis (from intrapulmonary or right-to-left atrial level cardiac shunting).
  - Equal ventricular pressures in Eisenmenger syndrome secondary to a VSD will not produce an audible murmur.
- Diagnosis is often delayed several years from onset of symptoms.
  - Secondary to progressive right ventricular dysfunction with inadequate systemic cardiac output
- Physical examination may be grossly normal but more advanced disease can present with
  - Hepatomegaly
  - Jugular venous distention
  - Peripheral edema
  - Loud second heart sound
  - Murmur of tricuspid regurgitation

Isolated Pulmonary Valve Stenosis

- Clinical manifestations on a continuum of degree of valvar obstruction
  - Mild narrowing of the pulmonary valve is associated with a crescendo systolic ejection murmur and absence of cyanosis.
  - In more advanced stenosis a harsher and later peaking murmur is common.
    - Associated with cyanosis from right-to-left shunting through a patent foramen ovale (PFO) or small ASD or from inadequate pulmonary blood flow in the absence of PDA.
    - Until closed, left-to-right shunting through the PDA can delay presentation of significant valvar stenosis.
  - <30% of newborns diagnosed with mild pulmonary valve stenosis will develop moderate or severe gradients.
    - Occurs in only 15% of those presenting after 1 month of age

Dextrorotation

- Can be diagnosed prenatally
  - Neonates are cyanotic at birth without associated respiratory distress.
    - Physical examination will be remarkable for cyanosis and possibly a ductal murmur.
    - Should otherwise be normal for a newborn.
  - SaO_2 will not increase significantly with supplemental oxygen (failed hyperoxia challenge test).
  - Care should be taken to assess lower-extremity pulses.
    - Coarctation of the aorta can be associated with dextro-looped transposition of the great arteries (d-TGA).
    - Prostaglandin E_1 infusion should be initiated once this defect is suspected.

Aortic Stenosis

- Valvar aortic stenosis can occur in isolation or be associated with subvalvar or supravalvar obstruction.
- With the exception of an audible click heard in valvular stenosis, the presentation and alteration of cardiovascular physiologic characteristics are very similar among the 3 defects.
- Mild to moderate stenosis.
  - Cardiac murmur may be the only sign of an abnormality in the newborn.
    - Ejection click followed by a harsh systolic ejection murmur
    - Best auscultated at the right upper sternal border
  - Additional signs and symptoms may not present until childhood.
    - Particularly in the pediatric population, mild to moderate aortic stenosis will not produce exercise intolerance, chest pain, syncope, or shock.
    - As a result, these patients are often referred to a pediatric cardiologist after the characteristic murmur is heard during a routine physical examination.
- Severe or critical aortic stenosis will present in the newborn as heart failure or clinical extremus.
  - Signs and symptoms of congestive heart failure will ensue.
    - Diaphoresis with feeding
    - Irritability
    - Lethargy
    - Fatigue
    - Acyanotic, but ashen pallor
    - Systolic ejection murmur of variable intensity and harshness
    - Diminished or absent peripheral pulses

Coarctation of the Aorta

- Auscultation
  - Systolic murmur is loudest at the left upper sternal border.
  - Murmur generally radiates to the back, medial to the left scapula.

- Neonates
  - Patient presentation tends to have a bimodal distribution.
    - Cases with diffuse arch hypoplasia are typically diagnosed shortly after birth.
    - Cases with an isolated discrete narrowing may not be diagnosed until later in infancy or childhood.
  - This lesion may not be detected by prenatal ultrasonography.
    - Therefore, palpation of the femoral pulses becomes a crucial part of the newborn examination.
    - When not palpable in an otherwise healthy-appearing newborn, upper-extremity and one lower-extremity blood pressure measurement should be obtained.
  - Blood pressure.
    - Must be checked in both arms; the left subclavian artery may arise proximal or (more rarely) distal to the coarctation site.
    - In the legs, a single-leg blood pressure should be adequate.
  - Determining presence of a PDA is of critical importance.
    - Because of the presence of ductal tissue in the aorta, coarctation cannot definitively be ruled out until the ductus has closed.
    - If the ductus is closed and a blood pressure gradient on cuff or narrowing on echocardiography is not found, a hemodynamically significant coarctation does not exist.
    - If there is concern about the existence of a coarctation, the patient should not be discharged until the ductus arteriosus has completely closed or close follow-up has been arranged.
- Adolescents
  - Distinctly different presentation from that in newborns and infants.
    - Multiple collateral arteries connect the aorta proximal and distal to the obstruction, thus bypassing the coarctation.
    - Intercostal arteries supplying the collateral artery system can become extensive and produce indentations or notching of the ribs.
  - Patients exhibit systolic murmur, upper-extremity hypertension, or both.
  - Upper- and lower-extremity blood pressures
    - May be a more accurate modality than Doppler flow for determining the clinical coarctation gradient

HLHS

- Newborns with HLHS can achieve normal birth weight and gestational age.
  - Fetal circulation can be adequately supplied by the right ventricle.
- Timing of diagnosis.
  - Unless HLHS is diagnosed prenatally and unless systemic saturations are monitored or cyanosis noted, the newborn with HLHS may not be diagnosed during newborn hospitalization.
    - Presentation is dependent on closure of PDA in conjunction with balance between pulmonary and systemic blood flow.
    - Such patients typically present with pulmonary over-circulation and systemic shock.
    - Profound systemic cyanosis may not occur until the SaO_2 falls below ~85% (possibly lower in dark-skinned children).
- Auscultation.
  - Cardiac murmur is commonly not present or appreciated.
- Palpation of femoral pulses.
  - Critical step in every newborn's routine evaluation
  - Commonly decreased in the newborn with HLHS
    - These pulses will become progressively weaker as the ductus arteriosus closes.
    - If aortic atresia exists, all 4 extremity pulses will diminish with ductal closure.

Tricuspid Atresia

- Patients have a similar physiologic display to those with HLHS.
  - Distinct types are classified based on relationship of great arteries, presence of VSD, and degree of associated pulmonary stenosis.
    - Tricuspid atresia with normally related great arteries with or without significant pulmonary stenosis
    - Tricuspid atresia and d-transposition of the great arteries

IE

- Clinical course.
  - Typically indolent
  - In rare cases, can cause cardiogenic shock
- Patients may have
  - Recurrent low-grade fever (90%)
  - Arthralgia (25%)
  - Gastrointestinal discomfort (15%)
  - Fatigue
  - Rigors
  - Other nonspecific findings

- Physical examination may be significant for
  - New cardiac murmur (rare)
  - Splenomegaly (55%)
  - Neurologic changes (20%)
- Classically described findings are rare in children.
  - Osler nodes (tender subcutaneous nodules on pads of fingers)
  - Janeway lesions (nontender hemorrhagic macules on palms or soles)
  - Roth spots (pale centered oval hemorrhages on retina)
  - Splinter hemorrhages in the nail beds
- Duke criteria for diagnosis of IE.
  - Criteria are met if a patient demonstrates
    - Both major criteria.
    - 5 of the 6 minor criteria.
    - 1 major and 3 minor criteria.
    - Overall, the minor criteria are often used when diagnosing pediatric IE.

Myocarditis

- Clinical presentation
  - Ranges from mild electrocardiographic (ECG) abnormalities in an otherwise asymptomatic child to fulminant congestive heart failure
- Less fulminant presentations
  - More typical in older children
  - 7–10 days after a viral upper respiratory infection or gastroenteritis
- Severe, fulminant onset
  - Cardiogenic shock may be present.
- Signs and symptoms
  - Fever
  - Malaise
  - Chest pain
  - Dyspnea
  - Pallor
  - Poor perfusion
- Auscultation
  - Muffled heart sounds
  - Gallop rhythm
  - Suggestive of congestive heart failure

Pericarditis

- History
  - Viral upper respiratory infection 10–14 days before the development of pericarditis is common.
- Physical examination
  - Pain in the left side of the chest
    - Worse in the supine position or with deep breathing
    - Relieved on sitting or leaning forward
    - May radiate to the left shoulder or to the neck
  - Fever (especially with bacterial pericarditis)
  - Signs of low cardiac output
    - Hypotension
    - Tachypnea
    - Tachycardia
    - Dyspnea
    - Pale, gray (sometimes mottled) pallor
    - Clammy skin
  - Auscultation
    - Pericardial friction rub (a biphasic sound) is the cardinal sign of early pericarditis.
    - With further accumulation of pericardial fluid, the friction rub may disappear and the heart sounds may become muffled.
  - With the onset of cardiac tamponade
    - Venous return during inspiration is compromised, resulting in a paradoxic rise in the jugular venous pressure (Kussmaul sign).
    - Cardiac output and systolic blood pressure decreases (pulses paradoxicus).
- Symptoms and signs depend on
  - Fluid volume within the pericardial space
    - The pericardial fluid can be serous, serofibrinous, hemorrhagic, or purulent in nature.
  - Rapidity with which the fluid collects
    - Rapid collection of fluid, as occurs in bacterial infections, may cause severe circulatory compromise (cardiac tamponade).
    - A gradually developing pericardial effusion allows the pericardium to stretch and, therefore, the increase in the pericardial pressure is slower and more readily tolerated.
  - Myocardial function
    - If myocardial function is depressed, even a gradual increase in pericardial fluid and pressure may cause significant circulatory compromise.

DCM

- Clinical presentation
  - Varies from progressive exercise intolerance with pulmonary congestion to systemic decompensation with complete cardiovascular collapse.
  - Diagnosis typically does not occur until the cardiac reserve is exhausted or nearly exhausted.
    - Often diagnosed after the patient experiences an acute viral illness that elevates resting metabolism enough to exceed the failing heart's compensatory mechanisms
- Physical examination
  - Consistent with congestive heart failure in symptomatic patients
    - Tachycardia.
    - Cachexia.
    - Sallow color.
    - Tachypnea.
    - Orthopnea (older children).
    - Hepatomegaly and weakened peripheral pulses may be found with severe cardiac dysfunction.
  - Auscultation
    - Gallop
    - Early systolic, regurgitant murmur of mitral regurgitation

HCM

- Presentation
  - Variable
    - Asymptomatic to congestive heart failure
  - Classic presentation
    - Syncopal patient with a loud cardiac murmur
- Physical examination
  - Typically normal
  - Progressive exercise intolerance
- Auscultation
  - Harsh systolic ejection murmur at the left sternal border with radiation to the neck.
  - If present, this murmur is accentuated when a squatting patient is asked to stand.
- History
  - Family history is critical.
    - Nearly one-half of all patients with HCM will have a first-degree relative with HCM or with a history of syncope or sudden death.

Miscellaneous Cardiomyopathies

- Arrhythmogenic right-ventricular dysplasia (ARVD)
  - Patients typically present with dysrhythmias.
- Mitochondrial cardiomyopathies
  - Often present early in life
  - Hypertrophied or (less commonly) dilated, poorly functioning heart
- Left-ventricular non-compaction cardiomyopathy
  - Cardiac dysfunction has a varying age of onset.
    - Newborn period to adulthood

DIFFERENTIAL DIAGNOSIS

- Peripheral pulmonary branch stenosis
  - Accompanied by a physiologic murmur.
    - Short, relatively high-pitched II/VI systolic ejection murmur
    - Auscultated equally on both sides of the sternum with diffuse radiation to both lung fields
  - Characteristic of the natural transition period from fetal to postnatal circulation.
    - Does not require urgent consultation
  - Most physicians are concerned that they may be missing the murmur produced by pulmonary stenosis.
    - This murmur is distinct from that of peripheral pulmonary stenosis in both its severity and focality.
    - Peripheral pulmonary branch stenosis is a softer, less intense murmur that is equally audible throughout the chest.
  - A murmur produced by significant valvar pulmonary stenosis will be
    - Harsh in character
    - At least grade 3 on a severity scale of 1 to 6
    - Often preceded by a valve click
    - Best auscultated at the left sternal border but will radiate to both lung fields
- Cyanosis
  - In most of these situations, a cardiac lesion is not the cause.
    - Pulmonary disease is more commonly the culprit.
  - Verify that cyanosis is truly present.
    - Acrocyanosis is a common occurrence in newborns, particularly in the setting of volume depletion or cool extremities.
    - Full-body cyanosis can occur in several scenarios, including respiratory distress syndrome.

- Pediatric hypertension
  - Any evaluation should include investigation for coarctation of the aorta.
- RCM
  - Care must be taken to distinguish RCM from constrictive pericarditis.

DIAGNOSTIC APPROACH

- In all heart lesions, the severity of the obstruction determines
  - Age at presentation
  - Clinical manifestations
- Foremost diagnostic tools.
  - History and physical examination
    - Signs of low cardiac output
  - Imaging
    - Electrocardiography
    - Chest radiography
    - Echocardiography
- All patients with Down syndrome should be evaluated by a pediatric cardiologist within the first month of life.

LABORATORY FINDINGS

- IE.
  - Blood cultures
    - Identical bacterial pathogens are identified before IE is diagnosed.
- Myocarditis.
  - The following values may be elevated:
    - Erythrocyte sedimentation rates
    - C-reactive protein
    - Leukocyte count
    - Platelet count
  - Measures of cardiac cell damage, including troponin I and creatinine kinase, myocardial fraction, can be used to establish that myocyte injury has occurred and then to monitor progress.
  - Verify the cause.
    - Serum viral cultures
    - Serologic titer assays
    - Polymerase chain reaction (PCR) amplification of the viral genome
- Pericarditis.
  - Determine the cause with
    - Total cell count
    - Differential cell count
    - Glucose
    - Protein concentration
    - Gram stain
    - Acid-fast stain
    - Cultures (with viral PCR as indicated)
    - Cytologic assays
- Fluorescence in situ hybridization and other modalities have increased incidence of documented gene malformations.
  - Some institutions obtain genetics consultation for all newly diagnosed congenital heart disease patients.

IMAGING

- Chest radiography
  - VSD and ASD
    - Generally noncontributory in diagnosing left-to-right shunt lesions before the onset of pulmonary over-circulation and the resulting pulmonary edema.
    - Once pulmonary over-circulation has developed, the cardiac silhouette will gradually increase in area and pulmonary vascular markings will become substantially more prominent.
    - Can also be used to help assess effectiveness of medical management, such as diuretic therapy.
  - Tetralogy of Fallot
    - The classic radiographic finding is the boot-shaped cardiac silhouette.
    - Relative right-ventricular hypertrophy in the healthy newborn often results in the erroneous reading of a boot-shaped cardiac silhouette on initial chest radiographic examination.
  - Ebstein anomaly
    - Marked cardiomegaly from right-atrial dilation
  - Dextrorotation
    - The classic radiographic finding for d-TGA is the *egg on a string*.
    - The great arteries are often oriented anteroposterior (the string) instead of perpendicular, removing the aortic and pulmonary knobs.
    - This great artery orientation can also create a mesocardia orientation of the cardiac silhouette, producing an egg-shaped silhouette.
  - Aortic stenosis
    - Chest radiography is helpful only if pulmonary edema has developed because of left heart failure.
    - The anteroposterior projection of the cardiac silhouette is usually not particularly helpful.

- Coarctation of the aorta
  - In the adolescent with long-standing, unrepaired coarctation, rib notching may be seen from engorgement of the intercostal blood vessels.
- HLHS
  - Unless pulmonary over-circulation occurs, radiography is unlikely to contribute to the diagnosis, except possibly to differentiate a cardiac from a pulmonary source of cyanosis.
- Myocarditis
  - Global cardiac enlargement and increased pulmonary vascularity with varying degrees of edema
- Pericarditis
  - May be normal when the pericardial effusion is small.
  - With a large effusion, the heart looks enlarged and has a globular appearance.
  - The pulmonary vascular marking may be prominent in patients with tamponade.
- DCM
  - Cardiomegaly with or without increased pulmonary vascular markings

■ Echocardiography

- VSD and ASD
  - 2-dimensional echocardiography will show a defect in the interatrial or interventricular septum and allow for determination of cardiac function.
  - Doppler flow velocities across the defect can estimate pressure differences between the respective chambers.
  - Together, this information can help guide timing and type of surgical correction, if indicated.
- Right-to-left shunting lesions
  - 2-dimensional and Doppler echocardiograms define cardiac anatomy, function, and direction of blood flow across any cardiac defects.
  - Doppler flow velocity across the RVOT allows estimation of outflow gradient, degree of obstruction, and any evidence of branch pulmonary artery stenosis.
- Pulmonary hypertension
  - Dilated right heart with right ventricular hypertrophy.
  - Pressure estimates that are commonly classified as sub-systemic, systemic, or supra-systemic.
  - PFO or ASD often allows blood to shunt from right atrium to left when right ventricular pressures are acutely elevated.
- Dextrorotation
  - 2-dimensional echocardiography will confirm the diagnosis and can evaluate the extent of intracardiac and extracardiac shunting.
  - ASD size, direction of ductus arteriosus shunting, and presence of a VSD are important components of inter-circulatory mixing.
- Aortic stenosis
  - 2-dimensional echocardiography is adequate to diagnose aortic stenosis.
  - Hyperdynamic systolic function of a hypertrophied left-sided ventricle may be found.
  - A bicuspid aortic valve will be present in nearly 60% of cases.
  - Doppler flow can approximate the systolic flow gradient across the obstructed region.
  - In the setting of subvalvar aortic stenosis, flow acceleration begins below the valve and can be associated with aortic regurgitation.
  - Supravalvar aortic stenosis is commonly seen with Williams syndrome and should prompt a search for the associated lesion of pulmonary branch stenosis.
  - In the neonate with aortic stenosis, patency of the ductus arteriosus and its direction of flow are important to help plan an appropriate management strategy.
- Coarctation of the aorta
  - To determine whether the coarctation is ductal dependent and to evaluate for other left-sided obstructive lesions
  - Used to diagnose the presence of a hypoplastic aortic arch or discrete narrowing of the aorta
- HLHS
  - Confirmatory study.
  - The sonographer should document presence or absence of PDA and flow through aortic and mitral valves, estimate the left-ventricular volume, determine size of the ascending aorta and ASD, and characterize the aortic arch and coarctation.
  - Size and competency of the pulmonary and tricuspid valves and right-ventricular function are critical information to obtain to stratify surgical morbidity and mortality risks.
- IE
  - Transthoracic echocardiography
    - Excellent specificity, but poor sensitivity limits its role in the diagnosis of IE.

  - Transesophageal echocardiography
    - Preferred visual diagnostic modality
    - Sensitivity of 80%–90%
    - Should be strongly considered in highly suggestive cases even if transthoracic echocardiography is negative
- Myocarditis
  - Global cardiac chamber enlargement with atrioventricular valve regurgitation and poorly contracting ventricles
- Pericarditis
  - Most frequently used to assess the size of a pericardial effusion, which can occur with pericarditis
  - Very useful in detecting evidence for cardiac tamponade and associated conditions (ie, myocarditis)
- DCM
  - Confirms diagnosis.
  - Dilated cardiac chambers, atrioventricular valve regurgitation, and depressed systolic function are nearly universal findings.
- HCM
  - Diagnostic method of choice
  - Type of hypertrophy (concentric versus asymmetric)
  - Ratio of interventricular septum to left-ventricular posterior wall thickness (>1.5 is diagnostic)
  - Presence of left-ventricular outflow tract (LVOT) or RVOT obstruction
  - Systolic anterior motion of the anterior mitral valve leaflet
- RCM
  - Distinguish RCM from constrictive pericarditis.
  - Echocardiogram shows normal ventricular size and function associated with dilated atria caused by the ventricular diastolic dysfunction.
- ARVD
  - Echocardiogram is diagnostic.
- Kawasaki disease
  - Evaluate for coronary artery aneurysms.
  - Confirm diagnosis.

■ Computed tomography, magnetic resonance imaging (MRI)
- Pericarditis
  - If echocardiogram is inconclusive.
  - Pericardial effusion is suspected to be loculated or hemorrhagic.
  - Distinguish from RCM.
- MRI for diagnosis of total or partial anomalous PVR in cases of complex anatomy

DIAGNOSTIC PROCEDURES

■ ECG
- VSD and ASD
  - ECG can be normal for age in patients with ASDs and VSDs.
  - However, as chamber dilation or hypertrophy occurs, signs of ventricular or atrial enlargement may develop.
  - Classic finding for patients with ASDs is an rSR' in lead V_1 from volume overload of the right ventricle.
  - ECG may be helpful for identifying the onset of pulmonary hypertension by the gradual development of right-ventricular hypertrophy.
  - Patients with complete ASD defect generally demonstrate a northwest, superior QRS axis and some element of ventricular hypertrophy.
- AVSD
  - Left axis deviation
  - Northwest QRS axis
  - Small Q wave in lead aVL
- Tetralogy of Fallot and pulmonary hypertension
  - Right-axis deviation
  - Tall R waves in the early or right-sided precordial leads
- Pulmonary atresia
  - Hypoplastic ventricles
  - Decreased voltage in left or right precordial leads
  - Abnormal QRS axes
- Ebstein anomaly
  - Right atrial enlargement
- Dextrorotation
  - ECG is generally unremarkable for a newborn.
  - Will not offer added information unless other cardiac defects exist.
- Aortic stenosis
  - ECG findings depend on disease severity.
  - In the newborn with critical stenosis
    - ST-segment elevation or depression, T-wave inversion, and sinus tachycardia may be present.
    - Right-ventricular hypertrophy is usually noted.
    - Voltage criteria for left-ventricular hypertrophy may already be present or develop quickly.

- Mild-to-moderate disease will probably demonstrate voltage criteria for left-ventricular hypertrophy, but ST- or T-wave changes are less likely.
- Coarctation of the aorta
  - ECG is unlikely to contribute to the diagnosis unless left-ventricular hypertrophy or strain is present.
- HLHS
  - A healthy newborn pattern of right-ventricular hypertrophy with a right-axis deviation may be more pronounced.
  - A distinguishing feature may be a relative paucity of left-ventricular forces.
- Myocarditis
  - A pathognomonic ECG finding is decreased precordial voltages consistent with a loss of functioning myocardium.
  - This finding can generally be differentiated from pericarditis by the absence of diffuse ST-segment elevation commonly present.
  - First-, second-, and third-degree atrioventricular block may develop, as well as wide-complex ventricular tachycardias.
- Pericarditis
  - Low-voltage QRS complexes with substantial pericardial effusion.
  - Changes caused by associated myocarditis, such as diffuse ST elevation in initial stages.
  - Gradually, the ST segment begins to normalize, with a decrease in the T-wave amplitude eventually leading to T-wave inversion.
  - These ECG changes may resolve completely, with the exception of T-wave abnormalities, which may persist for long periods.
- DCM
  - May show biventricular hypertrophy by voltage criteria with ST-segment and T-wave abnormalities
- HCM
  - ECG is abnormal in 90%–95% of cases.
  - Large voltages in the precordial leads suggest biventricular hypertrophy, ST-segment elevation and depression, T-wave inversion, and abnormally deep Q waves.
  - Occasional delta wave of Wolff-Parkinson-White syndrome.
  - Tendency for frequent episodes of ventricular tachycardia and ST-segment elevation on ECG during exercise.

- Cardiac catheterization
  - May be required with total anomalous PVR or partial anomalous PVR.
    - Particularly in cases of complex anatomy
  - The diagnosis can be difficult to confirm by echocardiography.
  - Distinguishes RCM from constrictive pericarditis.
  - Used to confirm diagnosis of pulmonary hypertension and guide medical therapy.
- Endomyocardial biopsy
  - Required for the definitive diagnosis of myocarditis
- Pericardiocentesis
  - Diagnostic and therapeutic
    - Pericardial fluid collection is large or rapidly increasing.
    - Bacterial pericarditis or when tuberculous pericarditis is suspected.
  - Drains the fluid to minimize the potential for clinical decompensation from tamponade
  - Allows possible etiologic diagnosis

CLASSIFICATION

- 6 grades of systolic or diastolic murmur severity
  - Grade 1
    - Barely audible and may require several cardiac cycles to detect
  - Grade 2
    - Soft but easily audible
  - Grade 3
    - Moderately loud murmur without a thrill
  - Grade 4
    - Loud murmur with a thrill
  - Grade 5
    - Loud murmur heard with the stethoscope barely off the chest
  - Grade 6
    - Loud murmur heard without the stethoscope touching the chest

TREATMENT APPROACH

- Prevention of disease progression
  - Consultation with a pediatric cardiologist if pathologic entity is suspected
- Determining whether surgical intervention is required
  - Preoperative management to maximize survival and minimize morbidity and mortality
  - Maintaining cardiovascular stability
  - End-organ perfusion and oxygen delivery
  - Multidisciplinary approach

SPECIFIC TREATMENTS

VSD and ASD

- Patients with known septal defects should be monitored closely for
  - Weight gain
  - Development
  - Clinical status
- Any signs of respiratory distress or failure to thrive will generally occur during the first 6 months of life.
  - Reevaluation by the pediatric cardiologist is indicated.
- Medical management.
  - Temporary improvement of complications may be achieved with
    - Diuretics
    - Afterload reduction
- Definitive prompt closure of an ASD or VSD.
  - Indicated when signs of pulmonary over-circulation develop

PDA

- In a healthy newborn or infant
  - Outpatient follow-up
    - Most PDAs close within days to months postnatally.
- Indocin
  - Standard treatment
    - If contraindicated or unsuccessful, PDA can often be ligated in the neonatal intensive care unit (NICU).
- Coil embolization
  - Indicated if persistent into childhood and a source of symptomatic left-to-right shunt
  - Performed in the catheterization laboratory
- Surgical closure
  - In the presence of decreased renal perfusion or pulmonary over-circulation

AVSD

- Surgical repair
  - Indicated for complete AVSD; includes
    - Patch closure of the ASD and VSD
    - Creation of 2 functioning atrioventricular valves from the single, frequently regurgitant common atrioventricular valve
    - Performed between 3–6 months of age to minimize the potential for irreversible pulmonary hypertension
  - Postoperative outcomes depend on
    - Severity of any residual atrioventricular valve regurgitation
    - Presence of pulmonary vascular disease
  - Partial AVSD
    - Can generally be repaired up to a few years of age
    - Low risk of pulmonary vascular obstructive disease

Arteriovenous Malformations

- Coil embolization
  - May reduce or reverse heart failure in many cases

Tetralogy of Fallot

- Tetralogy spell (hypercyanotic spell)
  - Uncommon but can be fatal if not treated urgently
    - Supplemental oxygen
    - Fluid boluses
    - Anxiolytics
    - Sedatives
    - Knee-to-chest positioning
    - Phenylephrine
- Tetralogy of Fallot without pulmonary atresia
  - NICU monitoring
    - Until ductus arteriosus (if present) closes.
    - Patients who can produce pulmonary blood flow to maintain SaO_2 >80% may be discharged from the hospital and allowed to grow.
  - Surgical repair
    - Tetralogy spell is a semi-urgent indication for repair.
    - In the absence of earlier unacceptable cyanosis (SaO_2 <75%), elective repair is performed at age 4–6 months.
    - Operative correction consists of patching the VSD and removing obstruction to pulmonary blood flow.
    - Resection or division (or both) of RVOT muscle bundles.
      - Depending on pulmonary valve and proximal artery anatomy, trans-annular patch after valvectomy to relieve distal outflow obstruction
    - The VSD is then patched.
    - Finally, depending on pulmonary artery anatomy, a patch is placed.
      - Supravalvar (main pulmonary artery)
      - Subvalvar (infundibular or outflow region)

- Trans-valvar (across the pulmonary valve annulus and extending into the supra and subvalvar regions)
- In many cases, a pulmonary valvectomy is performed during these repairs.
  - Progressive right-ventricular dilatation and eventual dysfunction are long-term morbidities that often require surgical or catheter-based pulmonary valve replacement.

- Tetralogy of Fallot with pulmonary atresia
  - Prostaglandin E_1 infusion
    - Maintains ductal patency until surgical repair
  - Surgical repair
    - If pulmonary artery size is favorable (>3 mm in diameter)
      - Complete repair can be performed in the neonate.
    - If pulmonary artery size is unfavorable (<3 mm in diameter)
      - An aortopulmonary shunt is placed to allow pulmonary artery growth until complete repair is performed later.
    - Patients without confluent pulmonary arteries who rely instead on multiple aortopulmonary collaterals
      - The collateral arteries can be unifocalized through a single or staged procedure to a conduit arising from the right ventricle.

Eisenmenger Syndrome

- Surgical closure of the septal defect
  - Will worsen the outcome if pulmonary hypertension cannot be ameliorated.
  - If not reversed, pulmonary hypertension can be fatal.
- Multiple approaches to decreasing pulmonary artery pressure and right-to-left shunting
  - Calcium channel blockers
  - Nitric oxide donors
  - Endothelin receptor antagonists
  - Inhaled oxygen therapy
  - Continuous infusions of prostacyclin (severe cases)
    - If the pulmonary vasculature proves to be reactive with these measures, surgical intervention may be considered.
- Lung transplantation or supportive symptomatic care
  - May be the only therapeutic option if the pulmonary vasculature does not respond to medications to decrease pulmonary hypertension

Pulmonary Hypertension

- Calcium channel blockers historically used for vasodilation, but use is now limited.
  - Extensive side effects.
  - <25% of pediatric patients continue to respond after 12 months.
- Oral sildenafil, bosentan, and prostaglandin I_2 analogues have become first-line agents.
  - Sildenafil, a phosphodiesterase-5 inhibitor, promotes vasodilation by accentuating the nitric oxide–mediated vasodilatory response in vascular smooth muscle.
  - Bosentan, a nonselective endothelin-1 receptor antagonist, inhibits vasoconstriction.
  - Epoprostenol, a prostaglandin I_2 analogue commonly viewed as the most potent extrinsic pulmonary vasodilator available.
    - Administered as a continuous intravenous (IV) infusion in children
    - Carries a significant side effect profile

Pulmonary Atresia

- Opening pulmonary valve
  - Balloon dilation or radiofrequency ablation to perforate through the valve cusps.
    - This approach is controversial and, in many institutions, surgical valvotomy is preferred.
  - If right-heart structures are significantly affected, the single-ventricle treatment route must be used.
    - Surgical specifics will be determined by the presence or absence of sinusoids.

Ebstein Anomaly

- Treatment consists of monitoring until the ductus arteriosus closes and PVR decreases.
  - At that time, the degree of forward pulmonary blood flow can be reassessed.
  - If pulmonary blood flow is adequate to produce SaO_2 >75%–80%, the newborn or infant may be discharged from the hospital.
    - PVR should continue to decrease with a commensurate increase in systemic SaO_2.
- Single-ventricle palliative surgery
  - Consider in newborns or infants with insufficient pulmonary blood flow.

Isolated Pulmonary Valve Stenosis

- Intervention is typically reserved for those patients with inadequate cardiac output or trans-pulmonary valve gradient >50 mm Hg.
- Balloon valvuloplasty in cardiac catheterization laboratory is well tolerated and risk of restenosis is low.

Total Anomalous PVR

- Surgical correction
  - Infracardiac drainage frequently becomes obstructed at some point along the extended, tortuous course of the vertical vein into the liver.
    - When present, constitutes a surgical emergency
  - Surgical correction for uncomplicated total anomalous PVR consists of reanastomosis of the pulmonary venous confluence to the posterior wall of the left atrium.
    - Common postoperative complications
      - Obstruction at the site of the anastomosis
      - Pulmonary vein stenosis
      - Left-atrial dysrhythmias

Partial Anomalous PVR

- Surgical correction may not be necessary unless symptoms develop (ie, exercise intolerance).
  - Unless ≥1 of the pulmonary veins returns anomalously, this anomaly rarely becomes hemodynamically significant.

Dextrorotation

- Preoperative management
  - Complex to manage in the newborn period.
  - The most important component is maintaining adequate atrial-level shunting.
    - Although the presence of a VSD is important when considering surgical options, ventricular-level shunting does not usually contribute a significant amount of intracardiac mixing in the newborn period.
  - Prostaglandin E_1 infusions.
    - Many patients with d-TGA have already begun receiving prostaglandin E_1 infusions at the time of diagnosis after failing the hyperoxia challenge.
    - Dosing ranges from 0.02–0.20 mcg/kg per minute.
      - Higher doses inherently increase the side effect profile.
      - PDA diameter cannot generally be titrated by changing infusion doses.
      - Once open, only doses of 0.01–0.02 mcg/kg per minute are usually required to maintain patency.
    - May be discontinued after assessing for paradoxical cyanosis (as seen with persistent fetal circulation), SaO_2, and arterial oxygen content.
      - Arterial oxygen content >30 mm Hg (typical fetal partial pressure of oxygen in arterial blood) with a corresponding SaO_2 >75%–80%, in the absence of metabolic acidosis, is predictive of adequate atrial-level mixing.
      - If these conditions are not met and the newborn demonstrates any signs of respiratory distress or pulmonary edema with marked cyanosis, the ASD is probably restrictive and needs to be enlarged.
    - Side effects of prostaglandin E_1 include
      - Apnea (Prophylaxis with caffeine or aminophylline may decrease risk.)
      - Irritability
      - Hyperthermia
      - Jitteriness
      - Decreased leukocyte function
    - High probability of intubation
- Catheterization procedures
  - Balloon septostomy (Rashkind procedure)
  - Blade septostomy
  - Radio-frequency ablation of the atrial septum
    - These procedures increase blood exchange and systemic oxygen delivery.
    - These lifesaving interventions can be associated with significant risks of morbidity and mortality.
- Surgical correction
  - Arterial switch (Jatene) operation
    - Surgical option of choice for most patients with d-TGA
    - Technically complex operation
      - Once the patient is placed on cardio-pulmonary bypass, the aortic and pulmonary arteries are transected above their native valves.
      - The surgeon removes the coronary arteries from the aortic root (arising from the right ventricle) by cutting small buttons of tissue surrounding the coronary artery's ostium.

- Similar-sized buttons of tissue are removed from the pulmonary artery (arising from the left ventricle), and the coronary arteries are sutured into the native pulmonary artery root (arising from the left ventricle).
- The aorta is freely mobile within the thorax and is easily sutured to the exposed pulmonary artery root.
- The main and branch pulmonary arteries remain attached to the lungs and are subsequently more restricted in their range of motion.
- To minimize surgical stretch and subsequent obstruction, the LeCompte maneuver is performed, which drapes the main and branch pulmonary arteries over the ascending aorta instead of underneath.

- Abnormal coronary artery anatomic configuration
  - Occurs in ~30% of all patients with d-TGA.
  - This abnormality can produce one of the major complications of the arterial switch operation.
    - A single coronary artery origin necessitates flipping of the button before reimplantation and is often associated with kinking and compromise of coronary artery flow.
  - Although no coronary pattern precludes a switch, transmural (coursing through the arterial wall) coronary artery anatomy and others may increase the risk of the procedure.
    - Alternative surgical approaches may be necessary.
  - Discordant annulus size of the great arteries can also produce difficulty.
    - Not usually a contraindication to an arterial switch
- Surgical outcomes
  - An overall mortality rate of 7% was reported in a study of 223 patients with d-TGA after the arterial switch operation.
    - Coronary artery pattern was not associated with an increased risk of death.
    - However, 2 studies with a total of 1,263 patients demonstrated a rate of coronary artery events between 7% and 8% over 15 years of follow-up.
  - Abnormal coronary artery vasomotor function has been demonstrated in asymptomatic children after arterial switch.
    - Patients require close postoperative follow-up.

Aortic Stenosis

- If diagnosed prenatally or shortly after birth in an otherwise healthy, stable newborn
  - Careful monitoring alone is justified.
  - Timely intervention on rapidly progressive stenosis can be planned before congestive heart failure and systemic shock occur.
- Right-to-left shunting through the ductus arteriosus suggests ductal-dependent systemic cardiac output (in the absence of persistent fetal circulation).
  - Patient should remain monitored in the hospital until a final decision about the need for intervention is reached.
- Balloon valvuloplasty
  - Standard of care for valvar aortic stenosis
    - Equally effective with less morbidity and mortality versus surgical valvotomy.
    - In most cases, aortic valvotomy results in some degree of aortic insufficiency.
    - Degree of insufficiency is usually mild and is well tolerated for many years.
  - Indications for non-emergent balloon valvuloplasty
    - Progressively severe left-ventricular hypertrophy with a trans-valvar gradient >50 mm Hg
    - Most cardiologists would also intervene in the presence of
      - Syncope
      - Exercise intolerance
      - Chest pain
      - Abnormal exercise stress test
- Surgical intervention
  - Indications
    - Stenosis is accompanied by significant valvar insufficiency.
    - Severe insufficiency develops after a balloon procedure with associated left-ventricular dilatation and dysfunction.
  - Surgical options
    - Valve replacement with a prosthetic mechanical valve
    - Cadaveric homograft
    - Porcine xenograft
    - Pulmonary valve autograft (Ross procedure)

- Important considerations
  - Patient age
  - Size
  - Lifestyle
  - Future adherence to an anticoagulation regimen

- Subaortic stenosis
  - With the exception of an absent valve click, subaortic stenosis is clinically indistinguishable from valvar stenosis.
    - However, blood flow velocity becomes accelerated before reaching the aortic valve and gradually damages the leaflets over time, which can result in progressive valvar regurgitation.
  - Surgical resection of this subaortic region is indicated to
    - Relieve obstruction.
    - Prevent progressive aortic valve damage and resultant insufficiency.
    - In general, surgical resection is performed with the onset of any degree of aortic insufficiency or outflow gradients between 20 and 40 mm Hg.
  - The decision to intervene is difficult.
    - Recurrence after resection is common.
    - Significant valve damage cannot be accurately predicted.
    - The rate of progression of subaortic stenosis is insidious and is not associated with acute cardiovascular decompensation.
  - Progressive valvar damage may ultimately require valve repair or replacement.
    - Homograft valve
    - Artificial valve
    - Autograft valve via the Ross procedure
- Supravalvar aortic stenosis (least common form)
  - When surgery is indicated
    - Patch aortoplasty of the narrowed region is corrective.
      - Reduces the coronary artery perfusion pressure and can produce coronary artery ischemia

Coarctation of the Aorta

- Initial treatment
  - Infusion of prostaglandin E_1 to maintain ductal patency or regain it.
  - Patient should receive no enteral feeds.
    - Possible intestinal under-perfusion
  - Renal function should be monitored closely.
- Discharged newborn or ductus closed at home insidiously, resulting in a coarctation
  - Shock is likely to be present from poor lower-body perfusion.
  - Patients should be treated similarly but will also require
    - Frequent blood gas monitoring for assessment and correction of acidosis
    - Possible mechanical ventilation
    - Upper- and lower-extremity blood pressures to track the success of the prostaglandin infusion in regaining ductal patency and possible inotropic support
  - If the clinician cannot reestablish adequate lower-body perfusion
    - Emergent intervention may be required.
- Balloon dilation
  - Gradient >20 mm Hg is generally considered the clinical indication for intervention.
  - Balloon dilatation results in splitting or tearing of intimal or proximal medial tissue planes.
    - Will often be repeated 2–3 times to ensure adequate luminal diameter
  - Stent placement during balloon dilatation reduces the rate of restenosis and provides significant relief from obstruction in adults.
  - Metallic stent placement is not recommended in young children; the artificial stent will not grow with the rapidly growing patient.
- Surgical management (standard of care)
  - Discrete coarctations
    - Subclavian flap repair
      - The subclavian artery closest to the coarctation (generally the left) is ligated distally and filleted open.
      - The coarctation region is also filleted open.
      - The flap of subclavian artery tissue is then rotated and sutured in place.
      - Less likely to result in aneurysmal dilatation of the segment of aorta, but until adequate arterial collateralization occurs, can be associated with a mild growth retardation and loss of strength in the respective arm.
    - Patch aortoplasty
      - Use of a Dacron patch to open the coarctation
  - Standard discrete coarctation and those associated with isthmic hypoplasia
    - Coarctation segment resection with extended end-to-end reanastomosis

- Coarctation associated with a diffuse segment of transverse arch hypoplasia
  - Not generally amenable to an extended end-to-end reanastomosis, except in specific circumstances

HLHS

- Prostaglandin E_1 infusion
  - Should be started immediately if HLHS is suspected.
    - Starting doses can vary widely based on clinical status, but all can result in apnea.
  - If cardiac lesion is strongly suspected, beginning prostaglandin E_1 infusion should not be delayed pending pediatric cardiology consultation.
- Arterial and venous catheters
  - Should be inserted if possible, when diagnosis is confirmed
- Parameters directing management
  - Renal function (assessed by urine output and serum creatinine)
  - Blood pressure
  - SaO_2
  - Arterial blood gases
- Strategies to provide adequate pulmonary and systemic blood flow
  - Hypoxia
    - Producing sub-ambient oxygen by increased nitrogen infusion into the inhaled gas mixture
  - Hypercarbia
    - Increasing carbon dioxide content of inhaled gas mixture
  - Permissive hypercapnia
    - When patient is intubated, decreasing minute ventilation with resultant pulmonary vasoconstriction
  - Decreasing systemic vascular resistance with vasodilatory medications
    - Milrinone
    - Nitroprusside
    - Phenoxybenzamine
- Surgical intervention
  - Surgical options depend on how blood flow is provided to the lungs and body.
  - The strategy for all single-ventricle hearts is based on 2 simple premises, regardless of which ventricle is hypoplastic.
    - A single ventricle cannot perform the function of 2 ventricles indefinitely.
    - PVR is elevated initially after birth and, in most cases, does not decrease completely for weeks to a couple months of age.
    - The physiologic characteristic does not change regardless of which ventricle is hypoplastic.
  - First-stage palliative surgery (Norwood procedure).
    - Produces a neoaorta from the main pulmonary artery and the hypoplastic ascending aorta.
    - Necessary but suboptimal.
    - PVR does not fully decrease for several months and requires systemic blood pressures to overcome elevated pulmonary artery pressures.
    - The right ventricle is then obligated to perform as a right and left ventricle and is also volume overloaded from shunt-mediated pulmonary over-circulation.
  - Second-stage palliative surgery.
    - Performed once PVR decreases.
    - Decreases the work of the single ventricle by removing the need for active pumping of the pulmonary blood supply.
    - The Glenn operation connects the SVC to the pulmonary artery, and the previously placed shunt or conduit is ligated.
    - Pulmonary blood flow is provided passively from the SVC into the low-resistance and low-pressure pulmonary arteries.
    - Systemic SaO_2 after the Norwood and Glenn procedures will generally remain 75%–85%, and patients typically have a higher hemoglobin concentration than acyanotic children.
  - Third-stage palliative surgery.
    - Fontan procedure.
    - Baffles the IVC to the pulmonary artery, routing all systemic venous return directly into the lungs.
    - Oxygen-rich blood is separated from oxygen-poor blood.
    - Systemic SaO_2 is typically near reference range (>90%).

Tricuspid Atresia

- Surgical correction
  - Unless the pulmonary stenosis protects the pulmonary vascular bed by limiting pulmonary artery pressure and flow, an initial procedure to limit pulmonary blood flow is necessary via pulmonary artery banding or ligation of the main pulmonary artery and placement of an aorto-pulmonary shunt.

- With closure of the PDA, presentation is similar to HLHS and tricuspid atresia requires creation of a neoaorta and placement of an aortopulmonary shunt via Norwood procedure.
- Timing and technique of the Glenn operation and Fontan procedure are the same as for HLHS.

IE

- A prolonged course of IV antibiotics is given to eradicate the high concentration of organisms deeply embedded in the fibrin-platelet matrix.
  - Duration of IV therapy will vary between 2 and 6 weeks, depending on bacterial speciation and antimicrobial sensitivity.
    - Blood cultures should be repeated during and after antibiotic therapy to ensure proper choice and duration.
  - For a complete review of the suggested regimen of antibiotic therapy, see the American Heart Association recommendations for IE therapy in adults (http://circ.ahajournals.org/content/132/15/1435).
- Once the patient has received adequate therapy and demonstrated several negative blood cultures, the infection can generally be considered cleared.
  - If no evidence exists of congenital heart disease or significant valvar derangement, continued evaluation by a pediatric cardiologist may not be indicated.

Myocarditis

- Treatment is largely supportive.
  - Although antiviral medications, corticosteroids, and IV γ-globulin are administered, limited and somewhat controversial data exist to support their use.
- Milder cases.
  - Bed rest
  - Hospitalization until the patient's cardiac status returns to baseline
- More severe cases.
  - Aggressive diuresis
  - Inotropy
  - Chronotropy
  - Afterload-reducing medications
  - Antiarrhythmic agents
  - Ventilator support
  - Mechanical circulatory support
    - Extracorporeal membrane oxygenation
    - Ventricular assist devices
- Patients who survive the initial phase but do not fully recover ventricular function or develop chronic heart failure will require long-term medical therapy.
  - Diuresis
  - Afterload reduction
  - Long-term antiarrhythmic medications
  - Automatic implantable cardioverter defibrillators (ICDs)
  - β-Blocker use in a heterogeneous pediatric population showed no significant outcome benefit.
    - In a subgroup with a morphologic left ventricle, there was a trend toward improved ventricular function.
- When patients do not respond adequately to medical or mechanical support
  - Cardiac transplantation is the only alternative for long-term survival in appropriately selected patients.

Pericarditis

- Management of pericarditis depends on
  - Size and cause of the effusion
  - Effect on cardiac function
- Purulent pericarditis
  - Urgent decompression
    - Lifesaving in patients with cardiac tamponade
    - Necessary for suspected purulent pericardial effusion
  - Percutaneous pericardiocentesis or surgical drainage
    - Large-bore pericardial drain or a surgically created pericardial window
    - Permits continuous drainage of purulent material
    - Prevents development of tamponade
  - Intrapericardial infusion of a fibrinolytic agent
    - Streptokinase decreases the recurrence of pericardial effusion.
  - Antibiotics
    - Given intravenously for 4–6 weeks
  - Partial or total pericardiectomy
    - Often necessary after treatment of purulent effusions to prevent development of constrictive pericarditis
- Viral pericarditis
  - No treatment other than a short course of anti-inflammatory medication, such as ibuprofen

- Pericarditis associated with other conditions
  - Treatment of the underlying condition leads to the resolution of the pericardial effusion.
    - Patients should be treated aggressively for all episodes of strep pharyngitis and receive appropriate procedural antibiotic prophylaxis.
  - Corticosteroids
    - Can be considered for persistent or refractory viral or secondary pericarditis

DCM

- Pharmacologic intervention
  - Treats the symptoms of congestive heart failure
  - Blunts the neurohumoral cascade
  - Aggressive diuresis
    - Spironolactone
    - Reduces pulmonary edema, hepatic congestion, excessive intravascular volume expansion
  - Angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers
  - Decrease morbidity and mortality.
  - Use is discouraged in the acute, decompensated period.
  - β-Blocker therapy
    - A recent multicenter, randomized, controlled trial in a heterogeneous pediatric population showed no significant outcome benefit with therapy.
      - There was a trend toward improved ventricular function in the patient subgroup with a systemic left-ventricular dysfunction.
      - Because of the limited enrollment sample and efficacy demonstrated by other smaller series, many cardiologists continue to use β-blockers as mainstay therapy.
  - Anticoagulation therapy
    - Aspirin
    - Warfarin
    - Commonly used to reduce the risk of thrombus formation
- Cardiac resynchronization therapy
  - Pacing modality used in patients with DCM and heart failure refractory to conventional medical management
    - Synchronizes ventricular wall motion.
    - Improves diastolic filling and systolic ejection fraction.
    - Reduces symptoms.
    - Use in children is limited by lack of controlled study data.
- Severe cases
  - Ventricular assist devices
  - Extracorporeal membrane oxygenation
  - Cardiac transplantation
    - May be indicated in appropriately selected patients if other treatment regimens are unsuccessful

HCM

- Symptomatic relief
- Minimizing the risk of fatal arrhythmias
  - Exercise stress tests.
  - 24-hour Holter monitoring to help stratify risk of ventricular tachycardia and sudden death.
  - Asymptomatic, nonsustained ventricular tachycardia on Holter monitor increases risk of sudden death 8–10 times.
- Pharmacologic intervention
  - β-Blockers
    - Indicated for patients who have symptoms or LVOT obstruction at rest.
  - If β-blockers are poorly tolerated
    - Calcium channel blockers have been shown to produce similar effects.
  - Amiodarone
    - Indicated when tachycardia is present
  - Prophylactic implantation of an automatic ICD is strongly recommended for patients with
    - Left ventricular wall thickness >3.0 cm
    - Family history of death related to HCM
    - Unexplained syncope
    - Nonsustained ventricular tachycardia on Holter monitor
  - Automatic ICD implantation as secondary prevention in patients with
    - Aborted sudden death
    - Documented ventricular tachycardia or fibrillation
    - Malignant ventricular ectopy
    - Now considered the standard of care
- Surgical myomectomy
  - Reduction of flow gradient in patients whose symptoms are related to their degree of LVOT obstruction
  - Brock operation or Morrow procedure
    - Reserved for symptomatic, medically refractory patients with a ventricular outflow tract gradient >50–60 mm Hg.
    - 10-year survival rate ~86%.
    - Intraoperative mortality rate can approach 5%.

- Medical septal reduction
  - Alternative to surgical myomectomy to improve LVOT obstruction
    - Infusion of desiccated alcohol into the septal perforating coronary vessels in the interventricular septum
  - Performed under transesophageal echocardiographic guidance in the cardiac catheterization laboratory
  - Advocated for patients with HCM who are failing medical management
    - Has been used with a resting ventricular outflow tract gradient as low as 40 mm Hg
  - Reduces the morbidity and mortality compared with surgery; however, risk is increased in
    - Coronary artery dissection
    - Uncontrolled myocardial infarction
    - Complete heart block (5%–10% risk) requiring pacemaker placement

RCM

- Generally unresponsive to conventional medical therapy.
  - Anticoagulation is indicated because risk of intracavitary thrombosis and stroke is increased.
- Patients should be referred for heart transplantation (HTx) once the diagnosis is made.
  - Pulmonary hypertension that is unresponsive to pulmonary vasodilators is the most commonly cited problem preventing HTx in these patients.

Miscellaneous Cardiomyopathies

- ARVD
  - Treatment is directed at preventing life-threatening arrhythmias.
    - Medications
    - Automatic ICDs
- Kawasaki disease
  - In the absence of cardiac involvement at either presentation or a 2- to 4-week follow-up appointment, further evaluation by a pediatric cardiologist is probably unnecessary.

Orthotopic HTx

- Standard therapy for end-stage congenital and acquired heart disease.
- Indications for HTx.
  - Infants
    - >75% of all recipients <1 year undergo HTx because of surgically irreparable congenital heart disease.
    - 17% of cardiomyopathy-related heart failure and dysrhythmias unresponsive to medical therapy result in HTx.
  - Adolescents
    - ~25% of 11- to 17-year-old HTx recipients have surgically irreparable congenital heart disease.
    - 62% of cardiomyopathy-related heart failure and dysrhythmias unresponsive to medical therapy result in HTx.
- Contraindications.
  - Absolute
    - Significantly elevated PVR
    - Elevated PVR unresponsive to vasodilatory therapy (ie, oxygen and nitric oxide)
    - Active cancer
    - Hepatic cirrhosis
  - Relative
    - Bacterial or viral infection
- The decision to proceed with HTx should be made on the basis of the individual patient's clinical status.
  - Cardiac catheterization
    - Determine hemodynamics and PVR.
  - Complete antiviral antibody titer panel
    - Exclude infection and guide use of antiviral medications postoperatively.
      - Herpes simplex
      - Cytomegalovirus
      - HIV
      - Epstein-Barr virus
      - Hepatitis A, B, and C
  - Panel reactive antibody testing
    - Assess the amount of circulating preformed antibodies in the recipient's serum.
    - May limit acceptable donor organs.
  - Social screening
    - Evaluate a potential recipient's emotional coping skills.
  - Financial screening
    - Verify that the financial burden of transplantation is minimized.
- Transplant status classification.
  - Strongly influences the expected waiting time for the recipient
    - Transplant status can change at any time if the clinical condition improves or worsens.
  - United Network for Organ Sharing (UNOS) status 1a
    - Generally several days to months before receiving a heart transplant, assuming survival is possible for this period.
    - Patient must be inotrope dependent and hospitalized.

- UNOS status 2
  - Depending on weight and blood type, infants >6 months can expect to wait up to several months.
  - Adolescents may require as long as 2 years before a suitable heart is located.

- Surgical procedure.
  - The donor heart is harvested in its entirety, with the exception of a cuff of posterior left atrial wall, which contains the pulmonary veins.
  - Once the recipient is placed on cardiopulmonary bypass, the heart is removed in a reciprocal fashion.
  - Anastomosis of the donor heart to the recipient is performed by a biatrial or, more commonly, a bi-caval (SVC-IVC) connection.
- Postoperative management.
  - Unique challenge of managing a patient with a denervated heart that has been ischemic for as long as 4 hours
  - Heart rate
    - Dependent on the intrinsic sinoatrial nodal rate.
    - Not influenced by the Valsalva maneuver, carotid massage, or atropine.
    - The resting heart rate of a transplanted heart is typically higher than that in reference controls.
      - However, it is often abnormally slow in the immediate postoperative period.
    - Isoproterenol.
      - Can be titrated to produce the desired heart rate
    - As the transplanted heart begins to recuperate from the surgical insult, heart rate and cardiac output will increase to meet the patient's needs.
  - Immunosuppressive medications
    - Typically started soon after the transplantation is complete.
    - The dosage is gradually decreased with time after transplantation.
      - Calcineurin inhibitor (ie, tacrolimus or cyclosporine) *plus*
      - Antimetabolite (ie, mycophenolate mofetil or azathioprine) *plus*
      - Corticosteroids
    - Side effects
      - Cyclosporine and tacrolimus: hypertension, nephrotoxicity, and derangement of the lipid profile (especially cyclosporine).
      - Azathioprine: neutropenia and hepatotoxicity.
      - Mycophenolate: lymphopenia and gastrointestinal distress (may require dose adjustment).
      - Side effects of corticosteroids have been well described.

WHEN TO ADMIT

- Same as when to refer (See next section.)

WHEN TO REFER

- Diminished or absent femoral pulses
- PDA murmur in the presence of decreased renal perfusion or pulmonary over-circulation
- Coarctation of the aorta
  - Pulses absent or thready
  - Lower-extremity blood pressures >15 mm Hg less than upper extremities
- Cyanotic heart lesion is suspected
  - Persistent hypoxemia (<70–80 mm Hg) despite adequate oxygen therapy
  - Failure of the hyperoxia challenge
- Progression of cardiomyopathy
  - Murmur
  - New gallop
  - Abnormal ECG or chest radiograph
  - Indicators of declining cardiac function
    - Weight loss or a plateau in weight gain
    - Missed developmental milestones
    - Fatigue
    - Activity intolerance
    - Personality changes
- HTx recipients who
  - Are febrile, immunosuppressed without an obvious, treatable cause
    - The transplant cardiologist should be involved to minimize the chance that graft rejection will be misinterpreted as a common, benign infectious illness.
  - Show signs of rejection
    - New-onset fatigue
    - Shortness of breath
    - Exercise intolerance
    - Low-grade fever
    - Vomiting
    - Diarrhea
  - Have unexplained abdominal distention, pain, or vomiting
    - Should prompt evaluation for an ileus or intussusception

- May also be a sign of intestinal angina caused by decreased cardiac output
- Have no chest pain
  - Absence of pain should not be comforting to the physician.
  - A denervated transplanted heart will not become significantly tachycardic in response to fever or pain.
  - A heart rate increase of only 10 beats per minute may indicate imminent cardiovascular collapse.

FOLLOW-UP

- Aortic stenosis
  - Once the newborn or infant is home, most pediatric cardiologists will arrange biweekly or monthly visits for the first 6 months of life.
  - During this rapid phase of somatic growth, changes in clinical status or aortic stenosis gradient can occur quickly.
  - When neonatal intervention is required, frequent return visits may occur for at least the first 6 months of life.
- After valve repair
  - Patients must be proactively managed in the postoperative cardiac intensive care unit.
  - Following AVSD repair, monitor for progression of residual postoperative mitral regurgitation or development of subaortic outflow tract obstruction.
  - Following balloon valvuloplasty in isolated pulmonary valve stenosis, periodic follow-up with a cardiologist to assess for recurrence of obstruction or development of pulmonary insufficiency.
- Coarctation repair
  - Routine cardiology follow-up is necessary to assess for possible longer-term morbidities.
    - Persistent systemic hypertension
    - Re-coarctation or arch aneurysm
    - Progressive aortic valve disease
    - Symptomatic cerebral aneurysms
    - Coronary artery disease
  - Complications include paradoxic hypertension or systemic blood pressure higher than preoperative measures.
    - β-Blockers are often used to treat hypertension in the immediate postoperative period.
    - When hypertension persists beyond the first few postoperative days, ACE inhibitors offset the renin-mediated phase of hypertension.
- Monitoring for rejection after HTx
  - Potentially life-threatening situation
    - Cellular rejection can begin within the first 5–7 days after transplantation.
    - Highest incidence during the first 3 post-HTx months.
  - Patients may exhibit
    - Malaise
    - Anorexia
    - Gastrointestinal distress
    - Low-grade fever
    - Nonspecific changes in sleeping patterns
  - If significant rejection is present, physical examination will reveal
    - Hepatomegaly
    - Mild elevation in heart rate from baseline
    - Possibly a new murmur or gallop
  - Patients require prompt evaluation and assessment.
    - Echocardiography to assess cardiac function
    - Endomyocardial biopsy if indicated
  - If disease proves the presence of rejection
    - Pulse steroids are administered.
    - Maintenance immunosuppressive regimen will usually be augmented.
  - Repeat biopsy.
    - Necessary to verify effective treatment for the rejection episode
  - Interventions (ie, scheduled vaccinations) that might upregulate the immune response.
    - Delay for ~3 months after resolution of the episode.
  - Frequent blood monitoring of HTx recipients.
    - Immunosuppressive agent side effects, such as neutropenia and hepatotoxicity

COMPLICATIONS

- Complications of HTx
  - First 6 months
    - Bacterial infections in 52% of patients
    - Opportunistic infections in 15% of patients
  - After 6 months
    - Immunosuppressive medications are decreased to maintenance dosing.
    - Predominant infectious organisms shift from bacterial to viral (83% of infections).
    - Specific microbes parallel those afflicting the general, non-immunosuppressed pediatric population.

- Long-term complications
  - Posttransplantation lymphoproliferative disease
    - Abnormal growth of lymphoreticular cells in immunosuppressed patients.
    - Occurs in ~5%–10% of pediatric HTx recipients.
    - Has been linked to primary posttransplant Epstein-Barr virus infection.
    - Most forms can be treated solely by a decrease in immunosuppression.
    - Some forms will require chemotherapy and possibly surgical resection.
  - Posttransplantation coronary vasculopathy
    - Progressive intimal and medial thickening of the transplanted heart's coronary arteries, with loss of coronary flow reserve and eventual luminal obliteration.
    - Risk increases with each episode of rejection (particularly after the first year), certain infections (ie, cytomegalovirus), original harvest time, and associated donor ischemic time; it is also increased in the presence of abnormal lipid profiles.
    - Statins (ie, pravastatin, atorvastatin) have been recommended in HTx recipients.
    - Freedom from posttransplantation coronary vasculopathy decreases with time from transplantation and with each decade of life after which transplantation occurs.
  - Newer immunosuppressant agents (ie, sirolimus) have shown initial promise as potential treatments for post-transplantation coronary vasculopathy; however, re-transplantation is the only definitive therapy.
- Immunization
  - Live viral vaccines
    - Should not be given.
    - The immunosuppressed patient's response to vaccinations will be blunted, particularly during the early post-HTx period.
    - Any systemic antigenic response may precipitate a rejection episode.
  - Non-live vaccinations
    - Should be given ~3 months after transplantation to minimize rejection.
- Immunosuppression
  - Predisposes these patients to serious infectious complications
    - However, deficiency in these medications places them at significant risk for rejection.

PROGNOSIS

- VSDs and ASDs
  - Natural history
    - Regardless of the mechanism, the PVR will reflexively increase in proportion to the degree of shunt volume (in ASD and VSD) and pressure (in VSD) to reduce stress on the arteriolar walls.
      - Over time, these pulmonary arterioles can become quite hypertrophied and cannot vasodilate.
      - This irreversible state of pulmonary arteriolar vasoconstriction results in pulmonary hypertension and eventual pulmonary vascular obstructive disease.
    - Small defects in the muscular portion of the interventricular septum often close spontaneously.
      - VSDs in other regions of the interventricular septum close less commonly.
    - The natural history of secundum-type ASDs depends largely on the initial defect size.
      - Nearly 85% <5 mm in diameter close spontaneously, compared with <2% when the defect is >8 mm in diameter.
      - Ongoing care is recommended to monitor for intermediate or late sequelae.
        - After VSD closure: subpulmonic stenosis or aortic insufficiency
        - After late ASD closure: atrial tachyarrhythmias
  - Patients at risk for pulmonary vascular obstructive disease
    - Those in whom VSDs neither close spontaneously nor are associated with pulmonary over-circulation
    - Those with an unrepaired defect and persistently elevated PVR (eventually can become irreversible)
      - As early as 6 months of age, particularly in patients with trisomy 21 (Down syndrome).
      - As early as 1 year of age in children without Down syndrome.

        - When pulmonary artery pressures exceed those of the left ventricle, the direction of shunted blood will become right to left, producing peripheral cyanosis (Eisenmenger syndrome).
    - Surgical mortality rates
        - <1% for both ASDs and VSDs
        - Device closure versus surgical correction of ASDs
            - Failure rate requiring surgical repair occurs in 4% of patients with devices.
            - Device-related complication rate is 7.2%; surgical complication rate is 24%.
        - Device closure of VSDs
            - Currently being performed in limited situations.
            - Success rates have been reported to be 99% but have been associated with a nearly 50% serious complication rate.
- Tetralogy of Fallot
    - Surgical outcomes
        - Pulmonary valvectomy performed during repairs leaves patients with some degree of pulmonary insufficiency.
            - Progressive right-ventricular dilation associated with pulmonary insufficiency is one of the sources of long-term morbidity in these patients.
        - Unifocalization of collateral arteries.
            - 10- and 20-year actuarial survival rates of 86% and 75%, respectively.
            - Freedom from repeat surgery is 55% and 29% at 10 and 20 years, respectively.
- Pulmonary hypertension
    - With currently available therapies, 10-year survival has increased to nearly 80%.
    - Untreated median survival is <4 years.
    - Death typically occurs from right ventricular failure or ischemia-induced dysrhythmias.
- Ebstein anomaly
    - Long-term outcomes are related to severity of disease (degree of cyanosis) at presentation.
    - Severely hypoplastic lungs will preclude cardiac palliation.
        - Most of these neonates die shortly after birth.
- Anomalous PVR
    - Natural history of prolonged untreated obstruction of the anastomosis or pulmonary veins
        - Irreversible pulmonary venous obstructive disease
        - Pulmonary vascular disease
        - Eventual right-heart failure
- Aortic stenosis
    - Progression rate
        - Unpredictable during the first 6 months of life
            - Final valvar gradients are poorly predicted by initial gradients.
        - Slower and more predictable after the first year
    - Patients not requiring intervention before 6 months of life are less likely to
        - Develop heart failure
        - Become critically ill during the follow-up period
    - After neonatal intervention
        - Frequency of restenosis is 15%–30%.
        - Aortic valvotomy results in mild aortic insufficiency, which is well tolerated for many years.
    - Subaortic stenosis
        - Recurrence rate is 20%–30% after resection.
    - Supravalvar aortic stenosis
        - Insidious disease progression marked by significantly elevated coronary artery perfusion pressures
- Coarctation of the aorta
    - 5%–25% rate of re-coarctation
    - The restenosis rate is <20% after balloon dilation.
        - Associated transverse arch hypoplasia is associated with a higher rate of reintervention.
    - Repair during or after adolescence is associated with a higher rate of persistent hypertension.
- HLHS
    - Sequelae include
        - Cardiac dysrhythmias
        - Cerebrovascular accidents with seizures
        - Myocardial ischemia
        - Pleural effusions
    - Patients may require multiple cardiac catheterizations.
    - Survival.
        - Improved survival after the Fontan procedure has been shown to be strongly correlated with shorter cardiopulmonary bypass and aortic cross-clamp times.
        - When the condition results in end-organ damage or a delay in surgical intervention, morbidity and mortality increase significantly.
        - Long-term prognostic data are lacking.

  - A palliative approach for single-ventricle physiological arrangement may ultimately serve as an extended bridge to cardiac transplantation.
    - 20%–30% of patients, after undergoing the Fontan procedure, develop heart failure, resulting in successful HTx or death.
  - Neurodevelopmental outcomes.
    - Most postoperative 8- to 9-year-olds had cognitive scores similar to those in the general population, but ~18% had IQ scores <70.
    - Some children have also had developmental motor delay and behavioral problems, including obsessive-compulsive disorder and attention-deficit/hyperactivity disorder.
- Tricuspid atresia
  - A single left ventricle is intuitively advantageous over a single right ventricle.
    - However, data have failed to demonstrate any differences in long-term survival.
- IE
  - Survival
    - Before the era of antibiotics, IE was universally fatal.
    - Today, survival has increased by 70%–80%.
  - Long-term prognosis
    - Primarily determined by the presence of complications.
    - If treatment is initiated early, valvar damage, heart failure, embolic events, and heart block can be prevented.
    - Prognosis is more guarded if IE involves a prosthetic valve or *Staphylococcus*.
- Myocarditis
  - Although its incidence is low in the pediatric population, accurate and timely diagnosis is critical for improving the related morbidity and mortality.
  - Mortality rates vary inversely with age of onset.
    - Nearly 75% of all newborns and infants who develop myocarditis will die of it.
    - In older children with less fulminant disease, the mortality rate is ~25%, with 50% exhibiting a complete recovery and another 25% becoming asymptomatic but having persistent abnormal cardiac function.
- Pericarditis
  - The pathologic course depends on the virulence of the offending organism.
- DCM
  - If unchecked, this change in myocardial structure and function can become irreversible.
- HCM
  - Morbidity
    - Ischemia-induced arrhythmias are the most likely source.
  - Mortality
    - Ventricular fibrillation is the most common cause of death in undiagnosed adolescents and young adults.
    - Overall risk of sudden death is 1%–2% per year (may be as high as 4%–5% in adolescents).
- RCM
  - Prognosis is poor.
  - Elevated left-ventricle end-diastolic pressures usually result in pulmonary hypertension and pulmonary vascular disease.
  - Death occurs within 1–4 years of diagnosis in symptomatic patients.
    - Pulmonary hypertensive crisis
    - Sudden death
- ARVD
  - Patients <30 years are at high risk for life-threatening ventricular tachycardias.
- HTx
  - Survival
    - Overall 50% survival at 13 years after transplantation.
    - Younger age at transplantation is associated with longer survival and decreased need for re-transplantation.
  - Quality of life
    - Although transplantation is a formidable treatment strategy for most patients and their parents, ~90% of HTx recipients surveyed at 1, 3, and 5 years after transplantation report excellent quality of life with no activity limitations.
    - Transplantation seems to be an acceptable treatment for patients with irreparable congenital or acquired heart disease.
  - Access to treatment
    - HTx is limited by the number of available donor hearts.
    - ~20%–30% of patients die while awaiting a suitable donor.

PREVENTION

- To ensure that no unnecessary or unknown risks are taken, exercise intensity, duration, and participation in any type of athletic event must be discussed among the
  - Health care team (including the cardiologist and pediatrician)
  - Patient
  - Family
- IE
  - Prevention is an integral step in caring for persons at risk.
    - Good oral hygiene.
    - Avoid unnecessary interventions.
  - Prophylaxis guidelines were recently updated and conditions previously included were eliminated.
    - Inappropriate prophylaxis can pose more risk than benefit when considering hypersensitivity reactions to antibiotics.
  - Conditions for which prophylaxis is reasonable include
    - Prosthetic cardiac valve or prosthetic material used for cardiac valve repair
    - History of previous IE
    - Unrepaired congenital heart disease, including palliative shunts and conduits
    - Completely repaired congenital heart disease defects using prosthetic material or a device placed surgically or by a catheter-based delivery system (during first 6 months following procedure)
    - Repaired congenital heart disease with residual defects at the site or adjacent to the site of the prosthetic patch or device (which inhibits endothelialization)
    - Cardiac transplant recipients who develop valvulopathy

DEFINITION

- Constipation
  - Infrequent elimination of large or hard stools that cause straining or pain
- In childhood, constipation not caused by another condition is known as
  - Idiopathic constipation
  - Functional constipation
- One expert consensus defined constipation as any of the following descriptions[1]:
  - Passage of hard, scybalous, pebble-like, or cylindrical cracked stools
  - Straining or painful defecation
  - Passage of large stool that may clog the toilet
  - Stool frequency <3 times per week, unless breastfed
- Can present as pain, fecal soiling, urinary tract infection, or enuresis

HISTORY

- Description of stools that child passes
  - Frequency
  - Consistency
  - Caliber
- History of stool withholding (A positive history strongly supports functional constipation.)
- Age of child at onset
  - If a newborn, whether newborn passed meconium in first day of life
- Toilet-training experience
  - Whether traumatic
  - Critical in toddlers and preschool children
- Diet history—how constipation began
  - With transition to cow's milk
  - During periods of high protein intake
  - With excessive cow's whole milk consumption
- Complications
  - Fissures
  - Bleeding
  - Abdominal pain
  - Anorexia
  - Enuresis
  - Urinary tract infection
  - Distention and vomiting (not caused by functional constipation)
- Prior evaluation and treatment
  - Over-the-counter medicines
  - Home remedies
  - Alternative therapies
  - Culturally specific therapies
    - Can be part of treatment plan if they pose no harm
- Change in urinary voiding pattern (possible occult spinal process affecting sacral nerves)
  - Stream
  - Continence
- Family history of
  - Heritable conditions
  - Functional constipation
- Specific questions to address differential diagnosis of
  - Hirschsprung disease (congenital megacolon)
  - Endocrine, metabolic, and neurologic disease
- In infants
  - Delayed passage of meconium

PHYSICAL EXAMINATION

Infants

- An empty rectum raises the possibility of Hirschsprung disease, particularly in conjunction with any or all of the following symptoms:
  - History of delayed passage of meconium
  - Explosive gush of stool on withdrawal
  - Hard impacted mass palpated in the pelvis or lower abdomen
- Impactions
  - Unusual
  - May indicate Hirschsprung disease
- External examination of perineal area
  - Establish the normal placement of anal orifice.
  - Look for
    - Anal fissure
    - Skin tag
    - Normal anal wink
- Examine lower extremities for
  - Tone
  - Strength
  - Symmetry
  - Reflexes
- Examine spine for
  - Dimple
  - Hair tuft
  - Vertebral anomalies

Children

- Check the child's growth parameters.
  - Recent growth velocity
- Assess physical appearance.
  - The child should appear well and not wasted or malnourished.
  - Abdomen should not be distended.
- Examination should establish presence or absence of fecal impaction in lower quadrants or the hypogastric area.

- External examination of perineal area.
  - Establish normal placement of anal orifice.
  - Look for
    - Soiling
    - Fissures
    - Skin tags
    - Normal anal wink in response to touch
- Rectal examination, with patient's cooperation.
  - With functional constipation, desiccated stool is found in the rectal vault.
  - Megarectum.
    - In older children with long-standing constipation
      - Chronic rectal distention may efface the internal sphincter along the rectal wall.
      - Anal canal will feel foreshortened.
    - In children who soil from chronic constipation
      - The disorder is sensory.
      - Tone of the internal sphincter should be normal.
  - Older child with functional constipation.
    - The rectum may be empty if the child has just defecated.
    - Carefully consider the possibility of Hirschsprung disease.
  - Be alert for extrinsic mass compressing the rectum (rare).
  - Patulous anus is indicative of a neurologic lesion or sexual abuse.
- Neurologic examination.
  - Explicitly assess lower extremities for
    - Tone
    - Strength
    - Symmetry
    - Reflexes
  - Analyze the patient's gait.
- Examine spine for
  - Signs of spina bifida occulta
  - Dimple
  - Hair tuft
  - Palpable vertebral deformity

DIFFERENTIAL DIAGNOSIS

Functional Constipation

- Despite the large number of possible diagnoses, at least 90% of affected children have functional constipation.
- Infants.
  - Parental definition of constipation in the first 6 months may be incorrect.
  - In otherwise healthy breastfed infants
    - Stool consistency rather than frequency is a critical determinant of constipation.
    - Straining and grunting (turning deep red) in producing a soft stool of average caliber is normal.
    - Mushy stool once a week requires no intervention.
  - Functioning rectoanal inhibitory reflex.
    - Manometric studies have documented this at birth.
    - Likely represents unsuccessful attempts to coordinate voluntary with involuntary defecation.
  - Treatment is required for the constipated infant who
    - Strains with production of a desiccated plug of stool followed by loose stool
    - Produces consistently desiccated stool of pebbly consistency
- Toddlers.
  - History of stool withholding is critical for diagnostic and therapeutic purposes.
  - Parents of toddlers are
    - Usually aware the child is constipated.
    - Frequently do not recognize stool withholding.
  - During typical withholding, the child may
    - Hide quietly.
    - Cling to an inanimate object.
    - Squeeze buttocks together.
  - Variations of stool-withholding behavior include
    - Crouching
    - Dancing or walking on tiptoes
    - Crying out in anticipation of pain
  - Episodes of withholding
    - Are misinterpreted by the parents as attempts to defecate.
    - Generate great concern in the parent.
- Children.
  - Once the child has attained privacy in the bathroom
    - Parents are not likely to be involved in toilet routine.
    - Constipation becomes occult.
  - Incomplete evacuation is common in school-aged children; typical scenario is
    - Child goes to the bathroom with regular or increased frequency.
    - Child passes only a small, hard piece of desiccated stool.

- Child emerges from bathroom not terribly bothered.
- Parent asks, "Did you go?" Child answers, "Yes." Both are happy.
- Pattern is punctuated episodically by the passage of a massive bowel movement.

- Children are often brought in, not for constipation itself, but for
  - Soiling
  - Recurrent abdominal pain
  - Blood streaks seen on stool
  - Excessive flatus
  - Anorexia
- Pelvic floor dyssynergia in children with stool withholding
  - Can affect urinary voiding dynamics
  - Predisposes child to enuresis or urinary tract infection

- Findings that support the diagnosis of functional constipation.
  - Onset after infancy
  - Presence of stool-withholding behavior
  - Episodic passage of large-caliber stools
  - Absence of red flags
    - Failure to thrive (weight loss, poor growth)
    - Vomiting
    - Abdominal distention
    - Persistent anal fissures, perianal disease
    - Persistent blood in stool or guaiac-positive stool
    - Delayed passage of meconium
    - Weak urinary stream, diurnal enuresis

Anal and Rectal Disorders

- Anal fissure.
  - May induce self-perpetuating cycle of withholding, worsening constipation, and reinjury
- Anterior ectopic anus.
  - Occasionally, the anal orifice is misplaced anteriorly, so that the stool bolus must turn anteriorly at the perineum.
  - Parents may report seeing a perineal bulge when the infant attempts to defecate.
  - Consider surgical reconstruction in children who fail to improve with medical therapy.
- Anal stenosis.
  - Characterized by straining during the production of small-caliber stools.
  - Frequently diagnosed during infancy.
  - Digital examination shows that the anal canal is narrow and not distensible.
- Anorectal malformations.
  - Rectal duplication
  - Anal trauma (abuse)
- Extrinsic masses, though rare, may intermittently or partially obstruct the rectum.
- Rectal duplication cyst.
- Pelvic mass, such as neuroblastoma, presacral teratoma, ovarian tumor, hematocolpos.

Neurologic

- Hirschsprung disease
  - The most common reason to consider Hirschsprung disease is failure of treatment for chronic constipation.
    - Appropriate in early infancy, when functional constipation is unusual and easily treatable
    - In the toddler and the school-aged child, more likely to reflect the complexity and duration of intervention required rather than a missed diagnosis of Hirschsprung disease
    - Findings with a very high negative predictive value for Hirschsprung disease
      - Almost all children with functional constipation withhold stool in response to the rectoanal inhibitory reflex.
      - This reflex is absent with Hirschsprung disease.
  - Hirschsprung disease should be considered in any child with refractory constipation who has had any of the following conditions:
    - Failure to pass meconium in the first 24 hours of life
    - Onset of constipation before 3 months of age
    - Symptoms of intestinal obstruction at any time (distention, pernicious emesis)
    - Lifelong dependence on laxatives, enemas, or mechanical manipulation to initiate defecation
    - History of enterocolitis in early infancy (sometimes misdiagnosed as gastroenteritis)
    - Associated syndromes such as trisomy 21, Waardenburg type 4, or congenital central hypoventilation
    - Failure to thrive or growth faltering
- Spinal cord lesions
  - Affect the second, third, and fourth sacral nerves.
  - Associated with sensory and motor deficits affecting defecation.
  - Congenital malformations (dysraphism, including spina bifida).
  - Tethered cord.
  - Trauma to sacral cord.

- Intraspinal and extra-spinal tumors.
- Consider when constipation is accompanied by abnormalities in bladder function or gait.
- Consider with visible abnormalities or palpable deformities of the lumbosacral spine.

- Cerebral palsy
- Neuromuscular diseases with hypotonia
- Refractory constipation
  - Frequently multifactorial and difficult to treat
  - Prevalent in children with
    - — Cerebral palsy
    - — Muscular dystrophy
    - — Generalized hypotonia
- Pseudo-obstruction syndromes
  - Characterized by intermittent episodes of functional intestinal obstruction.
  - Affect the neuromuscular function of the colon.

Metabolic and Endocrine

- Hypothyroidism
- Diabetes insipidus
- Hypercalcemia
- Hypokalemia

Medication and Toxin Related

- Antihistamines
- Anticholinergics
- Anticonvulsants
- Opioids
- Bismuth, aluminum hydroxide
- Tricyclic antidepressants
- Iron preparations (*not* iron-fortified formulas)
- Plumbism
- Infant botulism

Miscellaneous

- Celiac disease and cystic fibrosis should be considered in children with
  - Poor growth in weight or height
  - Recurrent respiratory symptoms
  - Anemia
  - Hypoproteinemia
- Cow's milk allergy
- Scleroderma
- Systemic lupus erythematosus

LABORATORY EVALUATION

- Routine laboratory tests
  - Not indicated in evaluating for functional constipation
- With growth failure, failure to thrive, short stature
  - Thyroid function tests
  - Celiac panel
  - Sweat test
- With delayed passage of meconium
  - Sweat test
- For refractory constipation
  - Thyroid function tests
  - Serum calcium
  - Potassium
  - Lead
  - Celiac panel
  - Sweat test

IMAGING

- Plain abdominal radiographs
  - Often do not have significant diagnostic value.
  - In functional constipation, should show dilated, enlarged rectum.
  - In Hirschsprung disease, should show empty rectum.
  - Can be used
    - — Selectively for confirmation that palpable abdominal mass is a fecal impaction
    - — For a questionable diagnosis in a child unable to cooperate with rectal examination
- Barium enema
  - In functional constipation, should reveal diffusely dilated colon and rectum.
  - In Hirschsprung disease, should reveal distal spasm, proximal dilatation.
- Magnetic resonance imaging of lumbosacral spinal cord for
  - Hair tufts, lipomas, hemangiomas overlying the lumbosacral spine
  - Abnormalities of gait
  - Abnormalities of urination
  - Absent anal wink
  - Absent cremaster reflex

DIAGNOSTIC PROCEDURES

- In infants with delayed passage of meconium
  - Anorectal manometry
  - Rectal suction biopsy
  - Unprepared barium enema
  - Sweat test
- Rectal manometry
  - Functional constipation: rectoanal reflex present
  - Hirschsprung disease: rectoanal reflex absent

TREATMENT APPROACH

- Goals of treatment
  - Establish a pattern of soft bowel movements at a regular frequency (at least 3 per week).
  - Wean the child from pharmacotherapy.
  - Have the child and family manage problem on their own with diet and behavioral modification.

- Involves laxatives, parental education, diet, and behavioral modification
- Considerations
  - Age of patient
  - Duration of symptoms and treatment
    - Transient constipation lasting several days
      - Typically can be managed with one to a few days of laxative use and dietary change
    - Functional constipation
      - Patients are affected for weeks to months before seeking medical attention.
      - Requires a phased approach and months of treatment.
      - In older children, may require 1–2 years of laxative therapy.

SPECIFIC TREATMENT

Infants

- Before the introduction of solids, add indigestible, osmotically active carbohydrates to formula/human milk.
  - Dark corn syrup or malt soup extract
  - Dose: 2–6 teaspoons per day, divided among several bottles
- Once juice and infant food are introduced
  - Give apple or prune juice and fruits.
- Infant glycerin suppositories
  - Can be used at the beginning of therapy to remove a desiccated rectal plug.
  - Should not be the mainstay of therapy because infants can become dependent on rectal stimulation.
- 2 studies have established the efficacy of polyethylene glycol (PEG).
- Constipated infants should *not* be treated with mineral oil—risk of pneumonia from aspiration.
- Treat externally visible anal fissures with petroleum jelly.

Toddlers and Older Children

- Functional constipation
  - Highly successful treatment adopted widely by pediatric gastroenterologists with published guidelines.
  - Divided into 3 phases.
    - Education and disimpaction
    - Maintenance
    - Weaning
  - Controlled studies have not documented greater improvement with biofeedback training than with standard treatment regimens.
- Education
  - Parents need to know
    - Constipation frequently engenders withholding.
    - Withholding is self-perpetuating.
    - Toddlers may require several months of laxative treatment that produces soft stools before they abandon withholding.
    - Long-term non-stimulant laxatives are safe, based on innumerable studies.
    - Non-stimulant laxatives that do not engender laxative dependence include
      - Mineral oil
      - Milk of magnesia
      - PEG
      - Lactulose
    - Reluctance to medicate children leads to premature discontinuation of therapy.
    - Experts discourage the prolonged use of stimulant laxatives (senna, bisacodyl), but limited use of senna is acceptable.
    - No proof exists that prolonged use of mineral oil impairs fat-soluble vitamin absorption.
  - Parents should be instructed to
    - Ignore withholding events as they would a temper tantrum.
    - Talk directly to toddlers and engage them in the therapeutic program.
    - Say, "I want you to push the poo-poo out of your body; don't hold it in. That's how you will get better, and it will stop hurting."
- Disimpaction
  - The goal of disimpaction is to remove all hard-formed stools throughout the colon.
  - Treatment begins with disimpaction for the patient who
    - Has had months to years of symptoms
    - Has an impaction on examination
  - For older children
    - Defer disimpaction until the weekend.
    - Treat with mineral oil to lubricate impacted stool.
  - Fiber is withheld during the disimpaction phase.
  - Enemas.
    - Once a day for 3–6 days.
    - Simple, effective, and safe (with important caveats).
    - Dose guidelines should be followed.
    - In the rare event of failure to pass stool following an enema, the child needs medical attention.

- Sodium phosphate enemas are contraindicated in children who
  - Weigh <10 kg
  - Have cardiac or renal impairment or electrolyte disorders
  - May have any form of intestinal obstruction
- Oral route versus enemas.
  - Oral PEG has been used successfully for disimpaction.
  - Choice should be made with the child's and family's input.
  - In 4- to 11-year-olds, comparison of daily oral PEG versus daily enemas for 6 days showed equal efficacy in resolution of fecal impaction.
- Laxative doses.
  - Rectal
    - Hypertonic sodium phosphate enema: 3 mL/kg/dose, once daily via rectum for 1–6 days
    - Mineral oil enema: 30–60 mL, once daily via rectum for 1–6 days
  - Oral
    - PEG electrolyte-free: 1.5 g/kg/d, maximum 100 g for 3 days
    - Mineral oil: 30 mL/y (1 oz/y) of age to maximum 240 mL (8 oz) twice daily for 3 days
    - PEG with electrolytes: 10–40 mL/kg/h, via nasogastric tube (maximum 2 L/h) until stool effluent clear

■ Maintenance
- Follows disimpaction and incorporates laxative use, dietary advice, and behavioral modification.
- Timely follow-up is essential.
- Laxative choice: Cochrane review supports mineral oil and PEG as superior to other agents.
  - Mineral oil
    - Contraindicated for children <2 years or at risk for pulmonary aspiration.
    - Parents should be counseled explicitly never to force a child to take mineral oil.
  - PEG
    - Cautions for mineral oil also apply for PEG.
    - PEG is an osmotic laxative widely used to treat functional constipation.
    - Polymer of ethylene glycol that is not absorbed or fermented by colonic bacteria.
    - Fairly tasteless, water-soluble powder that can be disguised when mixed into a child's drink.
    - Pediatric studies have established clinical tolerance, effective dose, and absence of unanticipated or serious adverse effects.
    - In a study comparing low-dose PEG with lactulose, no difference was found between the prevalence of abnormal electrolyte or nutritional parameters.
    - For severe pulmonary edema from PEG aspiration, bronchoalveolar lavage has been used successfully.
- Dietary fiber.
  - Addition of fiber is widely advocated as an adjunct.
  - A randomized controlled trial has shown benefits of fiber supplement when prescribed with a laxative.
  - Dietary changes that increase child's fiber intake include
    - Whole-grain breads and cereals
    - Increased fruit and vegetable intake
  - A recent systematic review of nonpharmacologic therapies concluded that therapies such as increased fluid, probiotics/prebiotics, physical activity, and yoga may be beneficial but require further study.
- Behavioral modification.
  - Toddlers
    - Focus on replacing stool-withholding behavior with deliberate attempts to defecate.
    - Defer toilet-training efforts until the child stops withholding.
  - Older children
    - Have the child sit on the toilet after meals for 5–10 minutes to capitalize on the gastrocolic reflex.
    - Reward success by use of a star chart.
    - Child should be rewarded for the targeted behavior: sitting.
  - Physician
    - Titrate laxative dose to achieve desired effect (soft bowel movement every day).
    - Work in partnership with the child and parents, who should report to physician frequently.

- Laxative doses (oral)
  - PEG electrolyte-free powder: 0.8–1.5 g/kg/d
  - Mineral oil: 1–3 mL/kg/d
  - Milk of magnesia: 1–3 mL/kg/d
  - Lactulose 10 g/15 mL: 1–2 mL/kg/d
  - Senna syrup 218 mg/5 mL: 10–20 mg/kg/dose at bedtime
- Weaning
  - Laxative therapy should not be stopped abruptly.
  - Some toddlers can be weaned after 6–12 weeks of maintenance treatment.
  - In older children, weaning may take 6–12 months.
  - Daily laxative dose can be decreased in 1 of 2 ways.
    - — Decrease to 75%, 50%, and 25% of initial dose over successive months.
    - — Give a full dose every second day for 6–8 weeks, and then every third day for another 6–8 weeks.
  - Efforts should be redoubled to
    - — Increase fiber intake.
    - — Foster compliance with behavioral program.
  - Older school-aged children should
    - — Be encouraged to practice self-monitoring of frequency and adequacy of bowel movements.
    - — Have a rescue plan (enema, suppository, or stimulant laxative) for a transient relapse.
    - — Consider no stool for >3 days a transient relapse.
- Common reasons for treatment failure of functional constipation
  - Inadequate disimpaction
  - Failure to escalate laxative dose to achieve 1–2 soft stools per day
  - Premature discontinuation because of the widely held notion that laxatives are addictive
  - Relying on dietary fiber alone

WHEN TO REFER

- Abnormal diagnostic studies.
- Findings that are inconsistent with functional constipation.
  - Growth failure
  - Distention
  - Vomiting
  - Bleeding
- Treatment is complicated by other significant problems.
  - Behavioral.
  - Emotional.
  - Parenting.
  - Mental health issues.
  - Toileting is the focus of a power struggle.
- Refer to pediatric gastroenterologist.
  - Infant who is refractory to treatment
  - Child who is refractory to treatment or cannot wean from laxative therapy after 12 months
- If Hirschsprung disease is suspected
  - Consult with surgeon and radiologist.
  - Decide on initial diagnostic test (rectal biopsy is the gold standard).

WHEN TO ADMIT

- Constipation associated with obstruction or enterocolitis
- Failure of disimpaction as an outpatient

FOLLOW-UP

- Toddlers and older children
  - Follow up by phone within 2 days of starting therapy.
    - — Ascertain whether the child is still passing hard stools.
    - — Titrate laxative dose to induce a daily soft bowel movement.
    - — Determine whether disimpaction is complete.
  - Question to determine whether disimpaction was thorough.
    - — Disimpaction failure is a common therapeutic mistake.
    - — Initial disimpaction failure undermines successful treatment because maintenance-dose laxatives will not penetrate or remove impaction.
    - — Failure should prompt a revisit to consider
      - Abdominal or rectal examination
      - Abdominal radiography
    - — Children who have extremely hard or treatment-resistant impactions can be admitted for nasogastric administration of PEG.
  - Remain optimistic and involved, because improvement beyond 12 months of therapy is well documented.

PREVENTION

- In infancy, human milk is highly protective.
- Dietary fiber is believed to have an important role in promoting regular bowel habit.
- Sufficient fluid intake to prevent dehydration.

REFERENCE

1. Adapted from Hyams J, Colletti R, Faure C, et al. Functional gastrointestinal disorders: Working Group Report of the First World Congress of Pediatric Gastroenterology, Hepatology, and Nutrition. *J Pediatr Gastroenterol Nutr.* 2002;35(Suppl 2):S110

Contact Dermatitis

DEFINITION

- Contact dermatitis is inflammation of the skin secondary to contact with an offending agent.
- 2 broad types.
  - Irritant contact dermatitis
  - Allergic contact dermatitis

SIGNS AND SYMPTOMS

- Clinical presentation of both types of contact dermatitis can be similar.
  - Range of responses
    - — Eczematous changes of the skin
    - — Pink, scaling, irritated plaques
    - — Severe vesiculobullous eruptions characterized by blistering changes of the skin and severe pruritus
- Irritant contact dermatitis
  - Can lead to lichenification.
    - — Accentuation of skin lines, often with hyperpigmentation, and an almost hardening of the skin
  - Acute irritant dermatitis occurs minutes to hours after exposure.
    - — Intensity of the reaction, related to
      - Nature of the chemical
      - Concentration
      - Duration of contact
    - — Conditions that foster a more severe reaction
      - Wet skin
      - Skin under friction, occlusion, or pressure
  - Solvent sniffers.
    - — Irritant dermatitis of the arms and chest
    - — Eczematous changes found mostly around the nose and mouth
- Allergic contact dermatitis—reactions can be
  - Bullous
  - Purpuric
  - Lichenoid
  - Papular
  - Urticarial
  - Pigmented
  - Hypopigmented
  - From plants, ie, poison ivy
    - — Linear arrays of vesicles where plant has come in contact with the skin.
    - — The genitals in young boys may be affected, because they transfer the allergen to this area when voiding.

DIFFERENTIAL DIAGNOSIS

- Atopic dermatitis
- Seborrheic dermatitis
- Tinea
- Psoriasis
- Rare conditions that can mimic diaper dermatitis
  - Acrodermatitis enteropathica from zinc deficiency
  - Letterer-Siwe disease

DIAGNOSTIC APPROACH

- The child or parent may be aware immediately of an offending agent.
- Use of a diary to chart symptoms and associated activities and exposures is recommended.
- If the irritant dermatitis is acute, identifying the culprit is often easy, given that it may be only a single agent.
- In chronic cases, multiple offenders are often present.
- Initial episode of allergic contact dermatitis may be easily identified because
  - The rash usually is localized to a specific area.
  - The history of the offending agent can be ascertained.

DIAGNOSTIC PROCEDURES

- Patch testing.
  - Application of suspected allergens to intact uninflamed skin.
    - — Substances are usually applied to the back and left on for 48 hours.
    - — After 48 hours, patches are removed and coded sites are evaluated for the presence of a reaction.
      - Erythema *or*
      - Bullae
    - — Some positive reactions may not show for up to 7 days; reevaluate at 5 and 7 days.
  - Commercially available patch testing system (23 common allergens) can be performed easily in the dermatologist's office.
  - In more extensive patch testing, individually prepared aluminum chambers with multiple allergens can be applied to the back with hypoallergenic tape.
- Photopatch testing to detect contact photoallergy is available.
  - The patch is applied, and after 24 hours the area is exposed to UV-A light.
  - The patch is read 48 hours later.

TREATMENT APPROACH

- Uncomplicated cases (for irritant and allergic contact dermatitis).
  - Topical steroids and emollients for milder disease
    - Elimination of the offending agent and liberal application of emollients is curative for mild irritant contact dermatitis.
  - Systemic medications, including oral corticosteroids and antihistamines for more dramatic presentations
    - Topical steroids are effective in allergic contact dermatitis but less so for irritant dermatitis.
- Identifying the causative factors so that they may be avoided is accomplished by good history taking.
  - In chronic cases, a parent or older patient may need to keep a diary.
- Complicated cases that may require skin biopsy.
  - No response to treatment in 1 month
  - Involvement of a large body surface
  - Severe reactions (eg, bullae)

SPECIFIC TREATMENTS

- Treatment of diaper dermatitis
  - Gentle application of protective barrier ointments, eg, zinc oxide and petrolatum
  - Lowest-potency corticosteroids
    - Can be used in severe cases 2–3 times daily for a limited time (3 days, no longer than 2 weeks).
    - Long-term exposure should be avoided in the occluded diaper area.
  - Care of diaper area
    - Bathing in water with minimal use of non-detergent soaps, followed by liberal use of emollients.
    - Barrier ointments should be used with each diaper change, with care not to produce excess friction.
    - Involved areas should be kept dry and free of urine and stool.
    - Caregivers should be encouraged to change the diaper frequently, as often as every 2 hours.
    - Commercial cleansing wipes, if used, should be fragrance and alcohol free.
    - Topical antifungal agents
      - Work well for secondary candidal infection of the diaper area.
      - Should be considered in irritant rashes that are present for >3 days.
- Treatment of allergic contact dermatitis, specifically, rhus dermatitis
  - Washing the skin and other items that may have come in contact with the plant.
  - If patient develops skin lesions, systemic antihistamines are usually needed.
    - Mild to moderate strength (class 7 to 4) topical steroids are appropriate.
    - Topical pramoxine (an antihistamine) is safe and can be used over large areas of the body 2–3 times a day.
    - If lesions are limited but very pruritic, a more potent topical steroid cream (class 1 or 2) can be applied for ≤2 weeks.
    - If lesions are more extensive, systemic steroid therapy for 2 weeks at a beginning dose of 0.5–1.0 mg/kg, followed by a rapid taper over the subsequent 2 weeks.
      - Short bursts of systemic steroids without tapering are often associated with rebound of rash.
- Rare severe cases of irritant dermatitis
  - Systemic steroids can be given for 2 weeks at a dose of 0.5–1.0 mg/kg with a rapid wean.
    - Short bursts of steroids without tapering are often associated with rebound of rash.
  - Topical or oral immunomodulators at the discretion of the dermatologist; data are limited.

WHEN TO ADMIT

- Severe contact dermatitis, as in a generalized contact dermatitis or systemic contact dermatitis.
  - Generalized contact dermatitis may occur with exposure to the smoke of a burning antigen (ie, *Rhus*/*Anacardiaceae* plant family).
  - Systemic contact dermatitis occurs when a patient is repeatedly exposed to a substance via oral, intramuscular, or intravenous (IV) route that cross-reacts with an allergen.
- Patients experiencing any
  - Fever
  - Chills
  - Nausea
  - Vomiting
  - Hypotension
- Secondary bacterial infection may require IV antibiotics if large body surface involvement exists.
- Although rare, secondary infection with herpesvirus may require IV antivirals.

WHEN TO REFER

- Presumed irritant contact dermatitis (including diaper dermatitis) that has persisted for ≥1 month despite aggressive topical treatment
  - Refer to a dermatologist.
- Involvement of a large body surface area or severe reactions (eg, bullae) or an atypical presentation
  - Refer to a dermatologist for skin biopsy.
- Patients in need of patch testing
  - Refer to a dermatologist or qualified pediatric allergist.

COMPLICATIONS

- Repeated episodes of irritant contact dermatitis that compromises the protective skin barrier may create a fertile environment for subsequent allergic contact dermatitis and skin infections.

PREVENTION

- Irritant contact dermatitis
  - Maintain the skin barrier.
    - By maintaining a healthy stratum corneum
    - By keeping skin well hydrated (but not overly) and well moisturized
  - Avoid irritants.
    - Parents and older children must be educated about common irritants (soaps/detergents, especially those with fragrance and dyes).
    - Formaldehyde, formaldehyde releasers, and other clothing treatments can aggravate skin; clothing should be washed before wearing.
- Allergic contact dermatitis
  - Identify trigger factors.
  - Educate the parent and older child about avoidance of triggers.
    - Patients and their families should be taught to identify poison ivy so that it can be avoided and removed, if possible.
    - Commercial nickel spot tests are available from several sources.
      - Patients may identify the presence of nickel in metal items with which they may come in contact.
    - It is often simple and best for the patient if the entire family eliminates the allergen.

DEFINITION

- *Exanthem,* meaning to bloom or to break out, refers to a skin eruption or rash that may be associated with fever.
  - Generally implies that the eruption is infectious in origin.
  - Extremely common in children, and rashes for different diseases may appear similar.
- Rubeola is also called "hard measles" or "10-day measles."
- Rubella is also called German measles or "3-day measles."
- Exanthema subitum ("sudden rash") is also known as roseola or roseola infantum, "rose rash of infants."
- Erythema infectiosum is also called fifth disease.

SIGNS AND SYMPTOMS

Viral Exanthems

Measles

- Incubation period for measles is typically 10–11 days.
- Prodromal illness characterized by increasing fever, cough, conjunctivitis, and coryza.
  - Fever commonly is high (40°C [104°F]).
- The measles exanthem is pathognomonic.
  - ~2 days before rash erupts, Koplik spots appear and increase in number until day 1 or 2 of the exanthem.
    - Tiny bluish-white spots on an erythematous base that cluster adjacent to the upper molars on the buccal mucosa
  - By day 4 of illness, rash erupts.
    - Deep erythematous macular rash begins on face and neck and spreads down the trunk and extremities.
    - Similar to that of rubella.
    - However, rash on the face and upper portion of the trunk soon becomes confluent to produce a characteristic morbilliform rash.
      - Rash seen with rubella tends to remain discrete.
- The combination of Koplik spots, fever, cough, conjunctivitis, and a morbilliform rash is sufficient to make a presumptive clinical diagnosis of measles.
- By day 6 fever subsides and rash begins to fade, leaving a faint brown pigmentation of the skin.
  - Fine desquamation ensues.
- Although usually very ill, children recover rapidly by day 8 or 9 of illness, often fully recovered by day 10 or 12.

Mumps

- Exanthem develops in <10% of persons infected with mumps virus.
- When present, lesions are maculopapular or morbilliform, pale pink, discrete, and concentrated on the trunk.
- The virus more typically involves the salivary glands, testicles (after puberty), pancreas, kidney, and meninges.
- Incubation period of 16–18 days.
- Clinical signs and symptoms develop in ~60%–70% of infected persons.
  - The remaining one-third have inapparent or subclinical infections, without salivary gland swelling.
- Illness typically begins with 1–2 days of anorexia, headache, and mild to moderate fever.
- Followed by pain around the ear and discomfort when chewing.
  - Diffuse but noticeable enlargement and tenderness of the parotid gland, often unilateral initially, then becoming bilateral in ~70%.
  - Other salivary glands may be involved.
- Parotitis can be distinguished from lymph node enlargement.
  - It extends anterior to the ear and below the ramus of the mandible posteriorly to the mastoid bone, usually obliterating the angle of the jaw.
  - Lymph nodes are more discrete and generally submandibular.
  - Differential diagnosis for parotitis includes
    - Other viruses (including HIV, parainfluenza types 1 and 3, enteroviruses, and influenza)
    - Bacteria
    - Noninfectious causes such as parotid duct stones, tumor, and Sjögren syndrome
- Erythema is commonly seen around the opening of the Stensen duct.

Rubella

- Incubation period for rubella is 2–3 weeks, with peak at 16–18 days.
- Period of maximal communicability is 1–2 days before and up to a week after onset of the rash.
- Typically clinical illness is mild and brief.

- Rash itself usually is the first sign of infection.
  - Typically a pink, maculopapular eruption beginning on the face and spreading downward to involve trunk and extremities.
  - Lesions remain discrete and pink, in contrast with the raised, confluent, and deeply erythematous macular papules seen with rubeola.
  - Facial rash clears as extremity rash begins.
  - Erythematous enanthema of pinpoint lesions or petechiae (known as Forchheimer spots) may occur on the soft palate.
    - Often indistinguishable from those seen with scarlet fever or rubeola
  - Complete resolution of the entire exanthem occurs by day 3–5 of illness.
- Fever is very mild (37.2°C–38.3°C [99.0°F–101.0°F]).
- Lymphadenopathy (usually posterior auricular and suboccipital lymph nodes) is frequently impressive.
  - Affected nodes are usually tender at the onset of the rash, but tenderness resolves rapidly over 2–3 days.
  - Although an important sign of rubella, lymphadenopathy is not specific.

Exanthema Subitum (Roseola)

- Roseola is characterized by
  - 3 or 4 days of high fever (40.0°C–40.6°C [104.0°F–105.0°F]).
  - Followed by abrupt resolution of the fever and development of a pink maculopapular rash.
  - Rash begins on the neck, sparing the face, spreading to trunk and extremities.
    - Lesions are discrete and last only for 1 or 2 days.
- Seizure may occur in a small number of infants and children during the febrile phase.
- Child usually has no other manifestation of illness and does not seem as ill as severity of the fever might imply.

Erythema Infectiosum

- Typical clinical presentation of erythema infectiosum.
  - Rash without fever or other systemic signs
  - Fever in 15%–30% of patients
- Nonspecific symptoms of malaise, myalgias, and headache followed by rash 7–10 days later.
- Rash first presents as bright erythema of cheeks and forehead with circumoral pallor ("slapped cheek" appearance).
  - Formed by confluence of many large macules and papules.
  - Palpable and hot to the touch but non-tender.
  - After a single day of facial rash, a maculopapular exanthem that may vary from faint to intense appears on the proximal extremities.
  - Rash spreads gradually to the trunk and distal extremities, leaving a reticular or lace-like appearance.
  - This second stage lasts 2–4 days.
  - In a third stage, rash may reappear transiently when skin is exposed to pressure, sunlight, or temperature extremes.

Enteroviral Exanthems

- Variable clinical manifestations because of the many enteroviral serotypes.
  - Associated rashes may be macular, papular, pustular, morbilliform, petechial, urticarial, ulcerative, or vesicular.
- Many echovirus and coxsackievirus serotypes.
  - Associated with generalized maculopapular rashes with discrete lesions similar to rubella
- Other enteroviral exanthems may mimic roseola infection.
  - Initial 2–3 days of fever followed by rash.
  - Enteroviral fever prodrome usually much lower than roseola.
- Maculopapular rashes predominate with enteroviral infections; however, vesicular lesions have been observed with enteroviruses, including coxsackievirus A5, A6, and A16, and echovirus 6.
  - The clinical syndrome known as hand-foot-and-mouth disease is commonly caused by coxsackievirus A16.
    - Exhibited by small erythematous macules that evolve into small vesicles on palms and soles
    - Often associated with discrete mouth ulcers (primarily involving gums, tongue, and inner cheek)

Infectious Mononucleosis

- In mononucleosis, lesions are discrete, pink to red macules or maculopapular with no specific distinguishing characteristic.
- Most often diagnosed based on other signs.

Varicella-zoster Virus

- Chickenpox
  - Lesions of varicella-zoster virus (VZV) infection in partially immune children differ from classic chickenpox seen prior to vaccine introduction.
  - These milder symptoms may include very few lesions that do not follow the typical pattern.

- Exanthem of varicella infection (in early classic or mild atypical form) can be readily confused with noninfectious conditions, such as insect bites, allergic dermatitis, drug reactions, and enterovirus or *Staphylococcus aureus* infections.
- Nonimmune individuals with primary VZV infection typically develop classic chickenpox.
  - Incubation period is 10–21 days, with symptoms starting around day 14.
  - 24- to 48-hour prodrome of mild, nonspecific symptoms prior to rash.
  - Rash begins as erythematous macules that develop into vesicles containing clear fluid, "dew drop on a rose petal."
    - Initial lesions form on scalp, face, and, occasionally, trunk.
  - Often intensely pruritic.
  - Within 2 days, fluid begins to cloud and lesions scab or crust.
  - As lesions begin to resolve, new vesicles erupt in stages over the trunk and extremities.
  - This pattern continues for 1–7 days in otherwise healthy children.
  - The number of lesions is usually ≤300 but can be >2,000 in severe cases.
  - Lesions resolve slowly over 1–2 weeks.
  - Fluid from open vesicles contains live virus; thus, transmissibility is decreased as lesions dry and form scabs.
- Reactivation (herpes zoster)
  - A localized vesicular exanthem in a dermatome pattern, related to the sensory nerve distribution containing latent virus.
  - Initial lesions resemble those of primary VZV infection but progress into larger, coalesced areas.
  - Usually associated with neuralgia and hyperesthesia in addition to pruritus.
  - New lesions can continue to appear for ≤1 week, followed by crusting and resolution over an additional 2 weeks.

Herpes Simplex Virus (HSV)

- Herpes simplex virus (HSV) causes vesicular exanthems and enanthems.
- Wide clinical variation based on age, affected body site, primary infection versus reactivation, mode of acquisition, and host immune status.
- Many HSV infections or reactivations (with HSV-1 or HSV-2) are asymptomatic.
- If lesions are apparent, they can be mucosal or cutaneous and may affect different body sites.
- Mucosal manifestations may be vesicular or ulcerative, are usually painful, and may be associated with nonspecific constitutional symptoms.
  - Mouth, pharynx, lips (vermillion or mucocutaneous border)
  - Eye (conjunctiva)
  - Female genital tract (vagina and adjacent structures, cervix)
  - Male genital tract (urethra)
- In young children, primary herpes gingivostomatitis is usually caused by HSV-1.
  - Presents as extensive, painful vesicles of oral mucosa and palate, with extension to the lip, tongue, and face
- In older children and adults, pharyngitis may represent primary HSV.
  - Can be difficult to distinguish from more common causes of pharyngeal edema and erythema (eg, group A β-hemolytic streptococci [GABHS], Epstein-Barr virus)
- Oro-labial HSV lesions (reactivation HSV) are quite common.
  - Usually seen as single or grouped, tender, vesicular lesions on an erythematous base at the vermillion border
  - Often preceded by paresthesias
- Ocular herpes, or keratoconjunctivitis.
  - Can be mild or severe and cause permanent corneal scarring with potential vision loss
- Cutaneous manifestations take a wide variety of forms.
  - Vesicular lesions are observed most often over skin near affected mucosal surfaces.
  - Lesions can develop on any skin area and have been associated with transmission of HSV during contact sports.
  - Can cause infection within an already disrupted skin barrier (eg, eczema herpeticum).
  - Can present as infection of the pulp or nail bed of a finger or toe ("herpetic whitlow").
    - May initially resemble bacterial cellulitis but usually follows vesicular or pustular lesions on the affected digit.
    - Symptoms are not responsive to antibiotics and usually progress to purple to gray discoloration of the digit.
  - A less common cutaneous presentation is erythema multiforme (EM).

- In the immunocompromised patient, including neonates, herpes simplex can be life threatening.
  - Disease may be more severe, more difficult to control (increased frequency of reactivation), or more likely to disseminate.
  - Mucocutaneous lesions ("skin, eye, and mucus membrane disease") may occur with or without more serious, life-threatening invasion (dissemination or central nervous system [CNS] involvement).
    - The lesions are vesicular, and virus can be isolated from specimens obtained from conjunctiva, oral mucosa, rectum, and skin lesions.
- Non-exanthematous manifestations can occur, including encephalitis, hepatitis, esophagitis, pneumonitis, and other disseminated forms.

Molluscum Contagiosum

- Typical molluscum contagiosum lesions are 1–6 mm.
- Discrete papules that can be skin-colored, erythematous, or translucent (and mimic a vesicle), sometimes umbilicated.
- Can occur in any cutaneous location but most common on face, eyelids, neck, chest, axillae, folds of the extremities, and genital region.
- Lesions may be linear because of autoinoculation.
- Associated dermatitis in the area of the papules in 10% of patients.

Bacterial Contagiosum

Meningococcemia

- Approximately two-thirds of patients with meningococcemia develop cutaneous manifestations.
- Incubation period is 1–10 days.
- Symptoms at onset may mimic a viral illness (fever, myalgia, headache, nonspecific constitutional symptoms).
- Erythematous, urticarial, or morbilliform macules and papules may appear.
  - Petechiae, pustules, and vesicles may also develop.
- Hallmark manifestations are purpuric lesions with jagged edges.
  - May progress to necrosis, ulcers, and eschars.
- With overwhelming meningococcemia, profound hypotension and shock.
- Purpura fulminans, purpuric and necrotic plaques combined with disseminated intravascular coagulation, is associated with significant mortality and morbidity (loss of limbs, digits, other body parts).
  - Invasive meningococcemia mortality is 8%–10%.

Mycoplasma pneumoniae

- Cutaneous signs are a minor manifestation of *M pneumoniae* infections.
- Maculopapular eruption may appear on the trunk and extremities of 10%–15% of infected persons.
- More common are rashes that result from an immune-mediated or allergic response.
  - Spectrum includes urticaria, EM, and vesicles or bullae.
- Patients often have had a prodromal illness of fever, headache, malaise, and cough.
- Pneumonia may be subclinical, with chest radiographic findings out of proportion to clinical presentation.

Scarlet Fever (Streptococcus pyogenes)

- Scarlet fever is a clinical syndrome of fever, pharyngitis, and rash.
  - Often with associated nausea, abdominal pain, and headache
- Characterized by a fine papular eruption on a brightly erythematous macular base.
  - Papular rash is typically concentrated on trunk and proximal extremities, likened to "fine sandpaper."
  - Transverse erythematous streaks of coalesced petechiae (Pastia lines) may be present, usually in the antecubital spaces.
  - Rash is commonly associated with prominent erythema of the lips, soles, and palms along with circumoral pallor.
  - Tongue may reveal prominent papillae on a very erythematous base, "strawberry tongue."
- During recovery phase, desquamation typically occurs and can resemble the peeling associated with mild sunburns.
  - May be more prominent at the fingertips and along the palms and soles

S aureus

- Common skin manifestations of community-associated methicillin-resistant *S aureus* (CA-MRSA) infections include impetigo, ecthyma, and folliculitis.
  - Limited to the epidermal layer of the skin or the hair follicles within this layer
- Erysipelas is usually caused by *S pyogenes*, but staphylococci must also be considered.
  - With erysipelas, skin appears erythematous and warm with some edema, usually associated by systemic symptoms, including fever and chills.
  - The superficial dermis and lymphatic channels are often involved.

- Cellulitis, now most commonly caused by *S aureus,* not *S pyogenes.*
  - Usually presents as erythema with some degree of purulence
  - Involves the epidermis, dermis, and subcutaneous fat layers of skin
- Superficial skin abscesses are the most common CA-MRSA–related skin infection.
  - Abscesses usually involve suppurative collection of fluid or pus in the cutaneous and epidermal layers of the skin.
  - Often coexist with cellulitis.
  - Boils and carbuncles (coalescence of multiple furuncles) are suppurative and often extend beyond epidermal layer to involve dermis or subcutaneous tissue.

DIFFERENTIAL DIAGNOSIS

- Clinical manifestations other than the rash must often be explored to distinguish one disease from another.
- Incubation period.
- Prodromal symptoms and signs.
- Patient age.
- Immunization history.
- Contact or exposure history.
- Distribution and progression of the rash.
- Evidence of other organ involvement.
- Pathognomonic signs (eg, Pastia lines, Koplik spots).
- Allergic and immune-complex diseases, such as childhood arthritis, can mimic infectious exanthems.
- Measles should be distinguished from
  - Kawasaki disease
  - Common infections from enteroviruses, adenoviruses, or Epstein-Barr virus
  - Bacterial infections (eg, *M pneumoniae*, streptococcal species)
- Kawasaki disease
  - Must be differentiated from scarlet fever, because coronary artery disease may be a complication that requires therapy in a significant number of children with Kawasaki disease.
  - Kawasaki disease can usually be distinguished by
    - Discrete bulbar conjunctivitis without exudate
    - Cracking of the lips
    - Tender lymphadenopathy (usually solitary, unilateral, and >1.5 cm in diameter)
    - Meatitis
    - Diarrhea
    - Changes in the extremities, including induration/edema with erythema of palms and soles
    - Desquamation typically involving the periungual areas and groin
  - These children are profoundly irritable, and fever persists >5 days in most.
  - As in scarlet fever, patients usually have erythema of the palms and soles, erythematous lips, and a strawberry tongue, with striking desquamation during the second and third weeks of illness.
- Scarlet fever
  - Important to distinguish streptococcal infections causing rash from staphylococcal infections causing similar manifestations.
  - *S aureus* produces a range of toxins, including an exfoliative toxin that may cause a scarlet fever–like rash with erythroderma and desquamation.
  - Differentiation is important to choice of antibiotic therapy, particularly with increasing prevalence of CA-MRSA.
- *S aureus*
  - Differential diagnoses associated with *S aureus* skin infections, specifically CA-MRSA, include *S pyogenes.*

LABORATORY FINDINGS

- Rubella
  - Virus is present in the pharynx within 5 days of onset of rash but is difficult to culture.
  - Serologic diagnosis is made by demonstrating an antibody titer rise between acute and convalescent sera taken 2–3 weeks apart.
- Infectious mononucleosis
  - Confirmed by peripheral blood smear and serologic tests
- Molluscum contagiosum
  - Diagnosis is typically made clinically.
  - However, scraping a characteristic papule and staining with Giemsa or methylene blue reveals a molluscum (Henderson-Paterson) body with direct microscopy.
- Meningococcemia
  - Cultures of blood and cerebrospinal fluid (CSF) are confirmatory.

SPECIFIC TREATMENTS

- Measles
  - Vitamin A supplementation should be considered for immunodeficient patients and patients 6 months–2 years who are hospitalized.
  - Limited data exist for vitamin A use in the United States.
- Chickenpox
  - Acyclovir may be used in certain groups to shorten disease course and limit eruption of new vesicles.
  - Herpes zoster: Antivirals may be indicated.
- Molluscum contagiosum
  - Lesions may resolve spontaneously over months, and watchful waiting is an acceptable plan.
  - Many parents will request treatment.
  - Therapy may alleviate discomfort, reduce autoinoculation, and limit transmission to close contacts.
  - Options include curettage or cryotherapy with liquid nitrogen.
    - Both are effective but may be traumatic for young children.
    - Curettage may also cause spread of lesions and scarring.
  - Application of cantharidin (blister beetle extract) or imiquimod cream are both off-label options.
    - Imiquimod cream is applied 3 times per day.
    - Contact dermatitis can be a problem with this therapy.
    - Facial lesions, in particular, can be treated with topical retinoids (eg, tretinoin) but may also have limiting side effects.
  - Severe disease in immunocompromised individuals can be treated with intravenous (IV) cidofovir; however, this agent is associated with known toxicities, including renal failure.
- Meningococcemia
  - Supportive management, including fluids and vasoactive agents, usually within a critical care setting, are often required.
  - Treatment with an empiric antibiotic, such as ceftriaxone, is required for adequate coverage of CNS as well as bacteria that cause sepsis.
  - Once *Neisseria meningitidis* is confirmed, definitive treatment is recommended.
    - 5–7 days of IV antibiotics should be given.
    - Close contacts within 7 days prior to presentation with invasive meningococcal disease are at high risk and should receive antibiotic prophylaxis, ideally within 24 hours.
- *M pneumoniae*
  - Macrolide antibiotics, doxycycline for those ≥8 years, and levofloxacin for older adolescents and adults
- Scarlet fever
  - Streptococcal infections are treated with penicillin or erythromycin.
  - Methicillin-susceptible *S aureus* infections can be treated with first-generation cephalosporins (cephalexin), penicillinase-resistant penicillins (dicloxacillin, oxacillin, nafcillin), or clindamycin (if susceptible).
  - Because of the high incidence of skin and soft tissue infections caused by CA-MRSA in the United States, trimethoprim-sulfamethoxazole (TMP-SMX) or clindamycin is often selected to empirically treat when CA-MRSA is suspected.
  - Note that TMP-SMX will not eradicate GABHS.
  - When possible, cultures from the focal infection site should guide antibiotic therapy.
- *S aureus*
  - For suspected CA-MRSA skin infections, use of clindamycin, TMP-SMX, or doxycycline is typically recommended.
  - Widespread clindamycin use has increased rates of clindamycin resistance among CA-MRSA.
  - Empiric antibiotic treatment needs to be based on local area antibiograms for MRSA isolates.
  - D-zone test is recommended for detection of inducible clindamycin resistance in erythromycin-resistant, clindamycin-susceptible isolates.
  - For purulent cellulitis, where there is purulent drainage or exudate in the absence of a drainable abscess, empiric therapy is recommended pending culture results.
  - In some cases of small abscesses (<5 cm) without evidence of systemic symptoms, incision and drainage alone without antibiotics may be sufficient.
    - Usually not recommended in an infant or young child or if infection is spreading quickly or involves multiple lesions

WHEN TO REFER

- Molluscum contagiosum
  - When the diagnosis is uncertain, if extensive disease is present or associated with poorly controlled atopic dermatitis, referral to dermatology or infectious disease specialists should be considered.

FOLLOW-UP

- All children who have measles should have careful monitoring; examiner should have a high degree of suspicion for secondary bacterial infections of upper and lower respiratory tracts.

COMPLICATIONS

- Measles
  - Acute complications usually related to inflammation throughout the respiratory tract.
    - Otitis media
    - Pneumonia
    - Bronchiolitis
    - Laryngotracheobronchitis
    - Difficult to distinguish clinically whether symptoms are caused by measles virus or secondary bacterial infections
  - Rarely, other organ systems may be involved, including CNS with acute encephalitis (1:1,000 cases of measles).
  - Subacute sclerosing panencephalitis (SSPE), also known as Dawson encephalitis, occurs because of persistent measles virus infection in the CNS.
    - ~4–11 cases of SSPE per 100,000 cases of measles in the United States, with increased risk if measles occurred at <2 years.
    - SSPE produces headache, vomiting, drowsiness, and personality or behavioral changes, progressing to symptoms such as seizures and coma.
    - In most, CSF reveals pleocytosis and elevated protein levels with high CSF measles antibody titers.
    - Prognosis is poor, with permanent neurologic sequelae and death commonly occurring within 1–3 years.
    - In rare exceptions, individuals show remission or reversal of symptoms.
    - Numerous therapies have been attempted; none has proven to be efficacious or curative.
- Mumps
  - CNS involvement, manifested as meningitis or encephalitis, occurs in ≥10% of cases, characterized by headache, nausea, vomiting, and mild nuchal rigidity.
    - It may occur before, during, or after the parotitis phase of the disease.
    - Course of CNS involvement similar to aseptic meningitis caused by other viruses; usually without sequelae.
    - In <2% of cases with CNS involvement, long-term neurologic sequelae or death.
    - CSF pleocytosis has been noted in ≤50% of cases with parotitis, despite >90% of individuals with mumps showing no clinical evidence of meningeal irritation.
    - Orchitis is uncommon in children, but unilateral involvement of testes and epididymis is observed in ~25% of male patients infected after puberty.
      - Patients with orchitis are usually quite ill; however, sterility rarely occurs.
    - Pancreas and other exocrine glands are rarely involved.
    - Kidney can be affected with resulting nephritis.
- Rubella
  - Complications are rare in younger children.
  - Arthralgias and arthritis develop in ~15% of adolescents and young adults.
    - Can last up to a month.
    - Arthritis rarely becomes chronic.
  - The most serious complications are usually related to congenital infections.
    - If mother is infected during the first trimester of pregnancy, there is a high probability that the fetus will become infected, causing multi-organ dysfunction or fetal demise.
- Erythema infectiosum
  - Rash usually resolves without any desquamation or pigmentation of the involved area.
  - Arthritis and arthralgia are uncommon in children.
    - Exanthem and arthritis are likely caused by immune complex deposition in the skin and joints.
  - Parvovirus B19
    - Has a predilection for infecting erythrocytes.
      - Mild myelosuppression can occur but typically goes unnoticed in healthy individuals.

- Life-threatening red cell aplasia may occur in patients with shortened erythrocyte survival (eg, sickle cell disease, hereditary spherocytosis).
  - Primarily caused by infection of erythroid precursor cells in the bone marrow, resulting in premature red cell lysis.
  - Clinical suspicion may be confirmed by
    - Testing for anti-parvovirus B19 immunoglobulin M in the immunocompetent patient
    - By polymerase chain reaction on blood or plasma in immunodeficient patients
  - Aplastic crises may require transfusion.
  - In immunodeficient patients with chronic infection, IV immunoglobulin therapy should be considered.

- Infectious mononucleosis
  - Ampicillin results in ~50% of patients developing a much more intense rash, which may also occur with other penicillins.
    - The ampicillin-associated rash is deeply erythematous and confluent, giving it a morbilliform appearance.
    - Resolves spontaneously within a week after discontinuing the antibiotic.
    - Rash in a patient treated for presumptive group A streptococcal pharyngitis is cause to reconsider the diagnosis.
    - Physician should reassure parents that this rash does not represent penicillin hypersensitivity.
- VZV
  - Chickenpox
    - Complications in immunocompetent persons can include
      - Most common secondary bacterial infections
      - Less common virus-related complications (eg, encephalitis; hepatitis; thrombocytopenia with hemorrhage; rarely, nephritis or arthritis)
    - Scratching can cause extensive excoriations, increasing the risk of secondary bacterial skin infections.
      - *S pyogenes* and *S aureus*, both of which can lead to concomitant disease (eg, impetigo, cellulitis, invasive soft tissue infections, toxin-mediated disease, life-threatening sepsis)
    - Immunocompromised hosts (eg, neonates, young infants) may exhibit more extensive and progressive disease.
    - 1%–4% of healthy children who receive varicella vaccine may develop mild, brief, atypical chickenpox rash (usually only a few lesions) within 1–2 weeks after vaccination.
      - Child is considered contagious, particularly if in contact with immunocompromised persons, until lesions are crusted or resolved.
  - Reactivation (herpes zoster)
    - Most common complication is postherpetic neuralgia.
    - More common in adolescents and adults.
    - Secondary bacterial infections can occur, as with primary VZV infection.

PREVENTION

- Measles
  - Transmission in the United States has been significantly decreased with the adoption of a routine 2-dose immunization schedule.
- Mumps
  - Prevention achieved through immunization, with a current 2-dose recommended schedule.
  - Unvaccinated or undervaccinated persons represent many cases occurring in the United States and worldwide.
  - More recent investigations have noted waning immunity to be a major contributor.
- Rubella
  - Since the introduction of the rubella vaccine in 1969, successful vaccination efforts have decreased infections from a high of 12.5 million in 1964 to <10 reported cases per year in the last decade.
  - Congenital rubella syndrome cases have been nearly eliminated in the United States.
- Meningococcemia
  - Effective vaccines exist for 4 of the 5 serogroups of *N meningitidis* responsible for most cases of meningococcemia (A, C, Y, W-135).
    - Includes meningococcal conjugate vaccines for use in persons 9 months–55 years of age
  - Routine recommendation for use exists for all adolescents 11–12 years of age with a second dose at 16–18 years of age.
  - Recommendations for immunocompromised and high-risk populations have been forthcoming.
  - There are 2 vaccines in the United States for prevention of serogroup meningococcal disease; recommended for adolescents >16 years.
  - All confirmed, presumptive, and probable cases of invasive meningococcal disease should be reported to the appropriate health department.

DEFINITION

- Cough can be described as a forceful exhalation.
  - Generally results from acute viral infection and is therefore self-limited
  - May be the harbinger of a more serious problem
- Cough can be exceedingly disruptive to the child and family.
  - It can lead to significant anxiety for all involved parties.
  - Allaying this anxiety through appropriate diagnosis and management is of prime importance.

HISTORY

Accurate Description of Cough

- Pattern and progression of symptoms
  - Duration
  - Frequency of discrete cough episodes
  - Quiet periods between cough (daily cough vs days or weeks between cough episodes)
  - Quality
  - Timing
  - Triggers

Age at Onset

- Chronic or recurrent cough that begins in early infancy, especially in infants <3 months
  - Congenital or anatomic origin
  - Requires a more aggressive approach toward evaluation
- Cough that begins relatively suddenly in toddlers
  - Foreign body aspiration
  - Requires active approach toward testing (bronchoscopy)
- Cough beginning at >6 months
  - May suggest airway hyperreactivity
- Cough beginning relatively suddenly in adolescents
  - Especially at times of psychosocial stress, might indicate a psychogenic origin

Family History

- Especially helpful with chronic symptoms
- Allergies, atopy, or asthma
  - Makes these diagnoses far more likely in the child with chronic or recurrent cough.
  - History of asthma or atopy in first-degree relatives increases the risk of asthma in the child by 2- to 4-fold.
- Family history of early childhood death related to infection
  - Makes an immune deficiency more likely

Neonatal History

- Preterm neonates are more likely than full-term neonates to have
  - Persistent airway hyperreactivity
  - Laryngomalacia
  - Gastroesophageal reflux
- Central nervous system sequelae are likely in neonates with
  - Poor Apgar scores.
  - Perinatal hypoxia.
  - Difficult postnatal course.
  - Suck or swallow dysfunction increases the risk of aspiration.
- Congenital abnormalities (eg, diaphragmatic hernia)
  - Pulmonary hypoplasia
  - Chronic respiratory dysfunction
  - Recurrent pneumonia

Environmental History

- Smokers in the household
  - Associated with significantly more respiratory infections and asthma symptoms in children
- Exposure to molds
  - Household water leaks
  - Decaying garbage
  - Ineffective cleaning of bathroom tile
- Dust mites
  - Old mattresses
  - Stuffed animals
  - Forced-air heating systems
- Roaches
- Mice
- Pets
- Exposure to other children
  - At school
  - At child care
  - Babysitters
  - Siblings

PHYSICAL EXAMINATION

- Physical examination plays a critical role in
  - Pinpointing the origin of the cough
  - Identifying signs of a more serious underlying chronic condition
- Nasal mucosa
  - Nasal speculum examination
    - Color and quality of mucosa.
    - Presence or absence of nasal secretions helps determine whether the cause of the cough is upper airway disease.

  - Rhinitis.
    - Pale, boggy, swollen nasal mucosa
  - Sinusitis (when symptoms are prolonged).
    - Associated maxillary or frontal sinus tenderness.
    - Pharyngeal drip with a cobblestone appearance (lymphoid hyperplasia) further supports the diagnosis of sinusitis.
    - Halitosis may also be present.
  - Chronic pharyngeal inflammation.
    - In the absence of other signs of acute infection, suggests gastroesophageal reflux
- Oral mucosa
  - Ulcerations or thrush suggest an immune deficiency.
  - Cough paroxysms triggered by a tongue depressor support the diagnosis of pertussis.
- Signs of an acute infectious process
  - Fever
  - Adenopathy
  - Pharyngitis
  - Rash
    - These do not necessarily rule out a predisposing condition, especially when the pattern of illness suggests chronicity or frequent recurrence.
- Thorough assessment of other body systems
  - Important in judging whether a more global workup is necessary
  - Clues to a more severe underlying process
    - Growth failure
    - Poor developmental milestone achievement
    - Clubbing
    - Heart murmur
    - Hepatosplenomegaly
    - Chronic lymphadenopathy
- Respiratory system
  - Stridor, inspiratory rhonchi, or wheeze.
    - Suggest upper and large central airway disease
  - Rales, expiratory rhonchi, and wheeze.
    - Indicative of lower or distal airway inflammation
  - Change in the quality of air exchange.
    - Can be an early finding in asthma and other diseases of airway obstruction
  - Accurate lower airway examination depends on the cooperation of the patient.
    - Wheeze and distal airway sounds can be masked by a patient's vocalization or crying.
    - A force of airflow insufficient to uncover milder changes may mask inspiratory and expiratory findings in infants and children who do not take deep breaths on command.
  - Every effort should be made to place the child at ease during the examination.
    - Game playing can be helpful.
      - Blowing on a feather
      - Blowing up a balloon
    - In younger children and infants
      - The examiner can mimic a forced expiratory maneuver by firmly but gently compressing the anteroposterior chest wall inward once the child has begun voluntary exhalation.
      - This approach will frequently uncover milder degrees of wheezing not appreciated with passive breathing.
      - The examiner should allow the infant or child to begin exhalation passively before performing this maneuver to ensure that the glottis is relaxed.

DIFFERENTIAL DIAGNOSIS

- Acute versus chronic (>3 weeks' duration) cough.
  - Chronic cough requires a more extensive evaluation plan.
  - Chronic or recurrent cough in infants <3 months suggests congenital or anatomic origin.
    - These infants are also at risk for bacterial bronchitis.
  - Chronic or recurrent cough beginning after 6 months of age may suggest airway hyperreactivity.
- Cough beginning with sudden onset.
  - In toddlers, aspiration is an urgent concern.
  - In adolescents, especially at times of psychosocial stress, may suggest a psychogenic origin.
- Upper, lower, or mixed airway origin.
  - Upper airway cough
    - Croupy
      - Young children with asthma (disease of the lower airway) may initially exhibit a croupy cough.
    - Throaty
    - Honking
    - Foghorn

- Lower airway cough
  - Productive with expectoration of sputum is classically the result of bacterial pneumonia.
    - Children with severe chronic sinusitis (disease of the upper airway) will frequently cough and expectorate or swallow thick sputum that may be blood tinged.

- Cough character can be a useful starting point.
  - Paroxysmal
    - Pertussis
  - Staccato
    - *Chlamydia* infection
  - Barking
    - Laryngotracheal infection
  - Throat clearing
    - Postnasal secretions
  - Honking
    - Psychogenic cough
      - Occurs during the daytime
      - Increases when more attention is paid to it
      - Does not limit or change with physical activity
  - Cough during feeding
    - Suggests swallowing dysfunction
    - Tracheoesophageal fistula with aspiration
  - Cough after feeding
    - Spitting up, retching, or arching of the back: gastroesophageal reflux
  - Associated fever
    - Respiratory tract infection
  - Cough worsening with exercise
    - Suggests reactive airways disease
    - Asthma
  - Night cough
    - Postnasal drip
    - Allergy
    - Sinusitis
  - Previous episodes, especially with seasonal variation
    - Allergy
  - Chronic cough with poor weight gain
    - More severe systemic illness
      - Cystic fibrosis
      - Immune deficiency

LABORATORY EVALUATION

- Acute cough rarely needs extensive laboratory assessment.
- Hematologic tests.
  - Complete blood cell count with differential
    - May help distinguish a bacterial from a viral cause if infection is suspected.
    - Localized infections, such as sinusitis, are not always accompanied by an elevated leukocyte count with a left shift.
    - Total eosinophil count may be an important clue to atopy.
      - Elevated immunoglobulin E level further corroborates the diagnosis of allergy and suggests the possibility of asthma.
- Nasal smear.
  - Positive result for eosinophils.
    - Corroborates the diagnosis of allergy and suggests the possibility of asthma
  - Increased polymorphonuclear leukocytes on nasal smear may suggest rhinosinusitis.
    - However, the result is difficult to quantify, and test may be misleading.
- Tuberculin skin test.
- Immunologic studies.
- α_1-Antitrypsin levels.
- Sweat chloride.

IMAGING

- Chest radiography
  - When cough is chronic and no clear diagnosis is evident on first assessment
- Computed tomography of the sinuses
  - Confirms the diagnosis of sinusitis in a complicated case
- Barium swallow
  - In infants
    - Anatomic causes of partial obstruction
    - Tracheoesophageal fistulae
    - Vascular rings
  - Modified for aspiration
  - Standard for gastroesophageal reflux
    - ~40% false-negative result rate

DIAGNOSTIC PROCEDURES

- Pulmonary function tests
  - Distinguish between
    - Upper and lower airways disease
    - Obstructive versus restrictive changes
  - Children must be old enough to exhale fully and inhale forcefully on command.

- Test should be reproducible to ensure accuracy and reliability of results.
- Airway tests.
  - Flattening of the inspiratory portion of the flow-volume loop.
    - Upper airway obstruction
  - Changes in the forced expiratory volume in first second of expiration to forced vital capacity (FVC) ratio or the forced midexpiratory flow rate over the middle half of the FVC (forced expiratory flow 25%–75%).
    - Airway obstruction consistent with distal disease
  - Reversibility of these changes (20% improvement) with a β_2-agonist confirms asthma and leads to effective therapy.
- Impulse oscillometry.
  - May be used in children 3–6 years old, too young for formal spirometry, to assess airways resistance and response to bronchodilator.
- Infant pulmonary function testing.
  - Can be used in infants
  - Less reliable
  - Requires a high level of expertise

- pH probe monitoring
  - The gold standard for diagnosing gastroesophageal reflux
    - Reserve for patients in whom primary empiric treatment fails.
- Bronchoscopy
  - Cough that begins relatively suddenly in toddlers.
    - To confirm foreign body aspiration
  - Useful to diagnose structural abnormalities of upper and lower airways.
    - Should be considered in patients with chronic symptoms not responsive to empiric treatment
  - If an upper airway origin is likely, flexible bronchoscopy can make a definitive diagnosis.
    - The bronchoscopist must always look beyond the vocal cords in this setting.
    - Preferred over laryngoscopy because lesions below the vocal cords can cause upper airway symptoms.
- Sweat test

TREATMENT APPROACH

- Treatment is based on the underlying disorder.
  - Empiric therapy, based on primary assessment, can be a reasonable starting point.
- Detailed history and physical examination are usually sufficient to reach an accurate presumptive diagnosis.
  - Response to empiric therapy will confirm this assessment.
- The cough as a symptom of an underlying condition should be discussed with the patient and family.
  - Treatment of the underlying disorder (if necessary) should always be the primary focus.
  - In some conditions, cough is an important component of the body's natural response to the primary illness.
    - Suppressing the cough, in the absence of effective therapy for the primary disorder, may worsen the problem.
- The decision to use a cough medicine as an adjunct to the treatment of the primary disease is left to the primary care physician and family.
  - When cough is limiting or otherwise debilitating the patient, symptomatic treatment may be reasonable.
  - Cold and cough medicines should not be used in children <4 years because of serious side effects, and they are ineffective in children <6 years.
- Honey may be beneficial to children >2 years.

SPECIFIC TREATMENT

Expectorants

- Despite widespread use, expectorants have not been shown to decrease cough in children.
- Guaifenesin (formerly glyceryl guaiacolate).
  - May be used to make secretions more fluid and reduce sputum thickness; however, the effectiveness of this treatment has been questioned.
  - Useful when drainage of secretions is important, as with sinusitis.
- Saline solution.
  - Safe adjunct to primary therapy.
  - Water is the most effective expectorant because expectorants work by increasing the fluid content of secretions.
  - Administration via nasal spray, inhalation, or orally.

- Older expectorants no longer prescribed to children because of their adverse effects.
  - Potassium iodide
  - Ammonium chloride

Mucolytic Agents

- Acetylcysteine
  - Previously used as a mucolytic agent to help liquefy thick secretions, especially in such diseases as cystic fibrosis.
  - Its propensity for inducing airway reactivity and inflammation has made it less popular.

Cough Suppressants

- Peripheral agents
  - Can be effective in transiently decreasing cough severity and frequency.
  - Demulcents (eg, throat lozenges) soothe the throat.
  - Topical anesthetics can be sprayed or swallowed; effects are short-lived, as oral secretions rapidly wash them away.
- Centrally acting agents
  - Narcotics
    - Effective narcotic agents commonly used in children include hydrocodone and codeine.
    - The metabolic clearance pathway of codeine in infants is immature and data for adults should not be extrapolated to children, particularly those <2 years.
    - Hydrocodone has a greater risk of dependency and no demonstrated advantage.
    - Should be used in older children with appropriate instructions and caution to avoid overuse or abuse.
  - Nonnarcotic medications
    - Dextromethorphan
      - Despite evidence in adults, data proving efficacy in children are lacking.

Decongestants (Pseudoephedrine)

- Topical or systemic
- Decreases nasal mucosal swelling
- Facilitates sinus drainage
- May work well in combination with expectorants to optimize treatment of chronic sinusitis
- Care should be taken in the use of these agents because
  - When used in excess, they have been shown to lead to tachyarrhythmias.
  - Topical nasal decongestants can cause rhinitis medicamentosa.
  - They have not been studied in younger children.
  - They should be avoided in children <6 years.
    - Intrathoracic pressure increases as a result of coordinated contraction of the expiratory muscles.
  - Use should always be limited to short periods to minimize these risks.

Antihistamines

- Can be helpful in the treatment of cough triggered by allergy.
- Minimal effect when cough is the result of viral or bacterial infection.
- May be detrimental because they can increase the thickness of secretions.
  - First-generation histamine receptor 1 antagonists may decrease nasal drip by exerting an anticholinergic effect.
- Diphenhydramine may have a modest direct effect on the medullary cough center.
  - The clinical benefits of these findings are unclear.

Bronchodilators

- Therapeutic trial of treatment with a β_2-agonist may be a reasonable first step in suspected airway hyperreactivity.

WHEN TO REFER

- When cough persists despite adequate therapy of primary disease
- When cough thought to be from hyperreactive airways is not easily reversible with β_2-agonist
- When cough recurs more frequently than every 6–8 weeks
- For cough associated with failure to thrive
- For cough associated with other systemic illness

WHEN TO ADMIT

- When the patient has respiratory distress
- When the infant cannot feed
- When associated with bacterial pneumonia not responsive to an oral antibiotic trial

Cyanosis

DEFINITION

- Bluish purple appearance of the skin or mucous membranes usually caused by increased concentration of deoxygenated (unsaturated or reduced) hemoglobin.
- Often indicates a significant reduction in oxygen concentration and may signify a life-threatening event.
- But acute cyanosis may well be benign.
  - Healthy newborn with acrocyanosis
  - When observed in the lips and fingers of a child who has been exposed to the cold, as in the ocean

PHYSICAL EXAMINATION

- Examine patient in a warm environment because cyanosis is made worse by vasoconstriction.
- The perception of cyanosis depends on the quality of ambient lighting and the examiner's ability to perceive subtle shades of blue.
- Cyanosis is observed most easily where capillary beds are close to the surface and arterial and venous blood are seen together.
  - Nail beds
  - Lips
  - Oral mucous membranes
  - Ears
  - Conjunctivae
  - Tip of the nose
  - Beneath the tongue
- In newborns, the best method for assessing cyanosis is to look at the tongue.
- Cyanosis can be present and location can help in determining the cause.
  - Peripherally
  - Centrally on the head and trunk
  - Differentially, with only lower parts of the body affected
- Acrocyanosis.
  - Bluish color in the hands and feet and around the mouth (circumoral cyanosis).
  - Mucous membranes generally remain pink.
  - In the newborn, a striking example of cyanosis arising from intense peripheral vasoconstriction and variable perfusion in the extremities compared with the central circulation.
  - The neonate with acrocyanosis typically does not have major changes in mental status during the event and appears well on physical examination.
- Tetralogy of Fallot (TOF).
  - Systolic murmur of pulmonic stenosis may be appreciated.
- Tricuspid atresia.
  - Increased left ventricular impulse, as opposed to other cyanotic heart diseases with an increased right ventricular impulse.
  - A murmur may or may not be present depending on restriction of blood flow through the ventricular septal defect (VSD) (a holosystolic murmur at the left lower sternal border) and the semilunar valves (a systolic ejection murmur).
- Total anomalous pulmonary venous return.
  - Auscultation of the heart may not reveal any murmurs.

DIFFERENTIAL DIAGNOSIS

Acrocyanosis

- May occur in infants when they cry, regurgitate, vomit, cough, or hold their breath
- Requires careful questioning and observation to differentiate it from serious underlying pathology
  - Seizure
  - Apneic episode
  - Cardiac arrhythmia
  - Congenital heart defect

Pulmonary Versus Cardiac Cyanosis

- Cyanotic heart disease may mimic respiratory disease and vice versa.
- Pulmonary cause suggested by
  - Tachypnea
  - Retractions
  - Nasal flaring
  - Grunting
- With a cardiac lesion, patients generally experience some respiratory distress but to a lesser extent than patients with underlying respiratory disease.
- Persistent pulmonary hypertension of the newborn (PPHN) as cause.
  - Difficult delivery.
  - Meconium-stained amniotic fluid.
  - Meconium aspiration.
  - Perinatal sepsis.
  - Asphyxia.
  - Low Apgar scores.
  - Because there is often a component of meconium aspiration pneumonia, these neonates demonstrate severe respiratory distress.

Pulmonary Disease

- Lower airways diseases (viral bronchiolitis, pneumonia, and status asthmaticus)
  - Cyanosis from ventilation-perfusion mismatching and small degrees of intrapulmonary shunt.

- Bronchiolitis, most often caused by respiratory syncytial virus (RSV), is associated with apnea that can induce cyanosis by hypoventilation.
- Pertussis
  - Caused by *Bordetella pertussis* or parapertussis.
  - In the paroxysmal phase, coughing paroxysms without interceding breath can result in deep visible cyanosis.
  - As the illness progresses, patients can turn blue after only a few coughs.
- Upper airway obstruction
  - Presents with inspiratory symptoms often manifested as stridor.
  - An infant with significant upper airway obstruction and stridor often demonstrates substernal retractions.
  - Worrisome symptoms include
    - Change in voice
    - Muffling or hoarseness
    - Difficulty in swallowing and handling secretions
- Croup
  - Usually from infection with parainfluenza virus
  - Less common agents
    - Influenza
    - Adenovirus
    - Measles
    - RSV
- Epiglottitis
  - Life-threating bacterial infection of the epiglottis and supraglottic structures.
  - Usually caused by *Haemophilus influenzae.*
  - Patients present with high fever, toxic appearance, and stridor.
- Aspiration of foreign bodies
  - Relatively common.
  - Can cause severe respiratory distress and cyanosis.
  - Suspect foreign body aspiration in an afebrile infant with acute onset of coughing, choking, stridor, or wheezing.
- Other causes of airway obstruction that may present with cyanosis
  - Laryngomalacia
  - Choanal atresia or stenosis
  - Subglottic stenosis
  - Tracheomalacia
  - Bacterial tracheitis
  - Obstructive sleep apnea

Heart Disease

- Pediatric heart disease of several different types can result in cyanosis.
  - With severe systolic and diastolic dysfunction of the left ventricle, as in acute myocarditis, elevated left atrial pressure can lead to pulmonary edema.
- Congenital cyanotic heart disease (CCHD).
  - A neonate with CCHD typically develops cyanosis in the first few hours of life.
  - Initially, cyanosis may be noticeable with crying or feeding, generally without evidence of respiratory distress.
  - Patent ductus arteriosus (PDA) serves as a means to
    - Deliver blood from the aorta to the pulmonary artery to be oxygenated in the lungs (left-to-right shunt) *or*
    - Maintain systemic blood flow (right-to-left shunt).
  - Many patients with CCHD deteriorate hemodynamically or become progressively more cyanotic as the PDA closes.
  - 4 groups of CCHD lesions.
    - Obstruct pulmonary blood flow with resultant shunting of blood from the right to left side of the circulation.
      - TOF
      - Pulmonary atresia
      - Tricuspid atresia
      - Pulmonic stenosis
      - Ebstein anomaly
    - Pulmonary blood flow may be normal or increased, but pulmonary venous return is anatomically separated from the systemic arterial circulation.
      - Dextro-transposition of the great arteries (d-TGA)
      - Total anomalous pulmonary venous return
    - Mixing of arterial and venous blood.
      - Truncus arteriosus
      - Double outlet right ventricle
    - Desaturation caused by dependence on right-to-left shunting through a PDA to maintain systemic perfusion.
      - Left-sided obstructive lesions of hypoplastic left heart syndrome (HLHS)
      - Critical coarctation of the aorta
      - Interrupted aortic arch

- Abnormalities of the right ventricular outflow tract.
  - TOF (most common congenital heart lesion that can cause cyanosis)
    - Consists of
      - VSD
      - Pulmonic stenosis
      - Right ventricular hypertrophy
      - Overriding aorta
    - Degree of cyanosis depends on the severity of the right ventricular outflow tract obstruction.
    - With more severe pulmonic stenosis, right ventricular pressure increases and blood is shunted across the septal defect from the right to the left ventricle, bypassing the lungs.
    - In neonates and infants with mild obstruction, symptoms of heart failure from the large VSD are likely to predominate.
    - Others may have severe cyanosis on closure of the ductus arteriosus.
    - TOF symptoms ("tet spells") may occur with vigorous crying or dehydration; affected neonates and infants initially become hyperpneic and restless as cyanosis increases.
      - The murmur of pulmonic stenosis softens and then disappears as pulmonary blood flow decreases.
      - The spell may precipitate a syncopal episode.
  - Pulmonary atresia with a VSD
    - More severe form of TOF that presents shortly after birth.
    - Prominent murmur of pulmonic stenosis characteristic of TOF is absent.
    - Neonates with pulmonary atresia and an intact ventricular septum have severe cyanosis that progresses as the ductus arteriosus closes.
    - Patency of ductus arteriosus is necessary for pulmonary blood flow in this lesion.
- Abnormalities of the tricuspid valves.
  - Tricuspid atresia
    - Blood from the right atrium travels through the patent foramen ovale from the right to the left atrium and then to the left ventricle.
    - From the left ventricle, blood flows via an unrestrictive VSD to the right ventricle and from there to the pulmonary artery.
    - Tricuspid atresia may be associated with normally related or transposed great arteries.
    - Saturation, degree of cyanosis, and blood flow depend on
      - Relationship of the great arteries
      - Size of the VSD
      - Presence or absence of pulmonic stenosis
    - If pulmonary blood flow is unobstructed, patients may have tachypnea and heart failure with minimal to no cyanosis.
  - Ebstein anomaly of the tricuspid valve
    - Involves the downward displacement of the valve leaflets into the right ventricular cavity.
    - Severity depends on the degree of displacement and ability of the remaining right ventricle to generate sufficient force to pump blood into the pulmonary arteries.
    - Newborns may have marked cyanosis, a holosystolic murmur with a gallop rhythm, hydrops, and pulmonary artery hypoplasia.
- TGA.
  - Most common cardiac lesion in neonates with cyanosis.
  - Neonates with TGA show severe cyanosis immediately after birth.
  - Left untreated, affected neonates progress from cyanosis to tissue hypoxia, acidosis, and death.
  - Unlike neonates with other cyanotic congenital heart lesions, these neonates have a normal volume of blood passing through the pulmonary bed.
  - Because their circulation is separated in parallel, they have little effective pulmonary blood flow and little effective systemic blood flow.
  - The degree of mixing between the separate circulations depends on the number and size of the anatomic connections.
  - Blood may shunt at the atrial, ventricular (if a VSD is present), or ductal level.
  - The typical neonate with TGA and an intact ventricular septum becomes progressively more hypoxemic as the ductus arteriosus closes.
  - Clinically, the neonate with TGA is likely to appear cyanotic but otherwise healthy, with a weight appropriate for gestational age.
  - Reverse differential cyanosis is rare but indicates TGA and a PDA with associated aortic arch anomaly or pulmonary hypertension.
- Truncus arteriosus.
  - Uncommon lesion.
  - Characterized by a single arterial trunk that originates from the heart and supplies the systemic, pulmonary, and coronary circulations.

- A large VSD is usually present, which allows total mixing of the 2 circulations.
- Degree of cyanosis depends on amount of pulmonary blood flow, which is determined by the pulmonary vascular resistance and any concurrent pulmonic stenosis.

- Total anomalous pulmonary venous return.
  - Pulmonary veins drain ectopically into the systemic venous circuit and ultimately into the right atrium, resulting in complete mixing of oxygenated and deoxygenated blood.
  - Site of connection can be supracardiac, infracardiac, or cardiac.
  - Maximal cyanosis occurs in neonates with an infradiaphragmatic connection, pulmonary venous obstruction, and a small atrial communication.
- Critical left-sided obstructive heart lesions.
  - Lesions include
    - Critical coarctation of the aorta
    - Interrupted aortic arch
    - HLHS
  - Affected newborns often look pale and poorly perfused and may demonstrate abnormalities in regional oxygen saturation on pulse oximetry.
  - Hypoperfusion from insufficient flow of blood into the systemic circulation results in hypotension and, with inadequate delivery of oxygen to the tissues, progressive metabolic acidosis.
  - With ductal-dependent systemic circulation, as the ductus arteriosus starts to close, the affected patient clinically deteriorates.
  - HLHS.
    - Closure of the ductus with HLHS often results in rapid cardiac arrest and death.
    - Diminished size and function of the mitral valve, left ventricle, aortic valve, and aortic arch results in severely diminished systemic circulation that depends on a wide PDA to supply blood to the body.
    - Structures distal to the ductal insertion into the aorta are dependent on the ductal flow; with absence of forward blood flow through the aortic valve, the coronary arteries and right arm also depend on the ductus via retrograde blood flow.
    - Arterial oxygen saturation (SaO_2) reflects mixing at the arterial level.
    - Venous blood returning from the systemic veins mixes in the right atrium with oxygenated blood coming from the left atrium via an atrial septal defect.
    - This mixed blood then travels through the right ventricle to the pulmonary artery and from there to the lungs and to the systemic circulation via the PDA.
    - Measurement of SaO_2 becomes crucial in trying to balance 2 parallel circulations.
    - Ideal saturation in this situation is ~75%, representing an approximate balance of blood flow into the lungs and into the systemic vasculature.
    - An acute rise in saturation could represent a preponderance of blood flow into the lungs to the detriment of systemic flow, resulting in acidosis and signs of systemic hypoperfusion despite the higher SaO_2.

Dyshemoglobinemias

- Dysfunctional hemoglobin that is unable to bind and deliver oxygen adequately is a cause of central cyanosis.
- Methemoglobinemia
  - Occurs when the iron in heme is in the 3^+ oxidation state and cannot bind oxygen.
  - Usually results from an oxidizing substance that changes hemoglobin Fe_2^+ to Fe_3^+, combined with the deactivation of the usual process for reducing methemoglobin back to hemoglobin.
  - Co-oximetry is the only accurate way to determine methemoglobin level.
- With carbon monoxide poisoning, significant tissue hypoxia can result from the increased affinity of hemoglobin for carbon monoxide compared with oxygen, but cyanosis is not usually apparent.
- Cyanide binds to the iron of cytochrome c oxidase, not hemoglobin.
  - Cyanide poisoning does not directly cause cyanosis but results in significant tissue hypoxia from the inhibition of oxidative phosphorylation.
  - When sufficient tissue hypoxia makes the muscles of respiration dysfunctional, cyanosis results from hypoventilation.

Miscellaneous Causes

- Sandifer syndrome
  - Children with significant gastroesophageal reflux sometimes have paroxysmal acrocyanosis (especially perioral) in association with
    - Brief episodes of limpness or tonicoclonic motions suggestive of a seizure
    - Apnea

- Prolonged generalized seizures
  - Often associated with impaired respiration
- Neuromuscular disorders causing weakness of respiratory muscles
  - Spinal muscular atrophy.
  - Botulism.
  - Congenital myopathies.
  - Metabolic disorders.
  - These conditions can result in hypoventilation followed by collapse of lung units resulting in hypoxemia.
- Cyanotic breath-holding spells
  - History of crying, typically followed by sudden breath-holding in forced expiration with apnea and cyanosis.
  - May progress to limpness and loss of consciousness.
  - Cyanosis can appear faster than anticipated with simple breath-holding.
  - Loss of tone is often striking.
  - Cyanosis resolves as the child resumes normal breathing.

Cyanosis in the Newborn

- Acrocyanosis of the hands and feet is common in the first 6–24 hours of life; usually of little significance.
- Central cyanosis persisting beyond the first few minutes of life necessitates further evaluation.
- Newborns with persistent cyanosis or hypoxemia despite oxygen administration may have
  - CCHD
  - Primary lung disease
  - Pulmonary artery hypertension
- By 24 hours of age, a hemoglobin oxygen saturation <95% in the lower extremities warrants further investigation.
- Comparing arterial blood saturation proximal and distal to the entrance of the ductus arteriosus into the aorta helps determine the origin of cyanosis in a newborn.
- PPHN.
  - High residual pulmonary vascular resistance reduces pulmonary artery blood flow to the lungs with concomitant persistence of shunting from the right to the left side of the circulation through the ductus arteriosus and foramen ovale.
  - Oxygen content of blood in the left atrium is decreased as a result of mixing desaturated venous blood that has crossed the foramen ovale with oxygenated blood that has traversed the pulmonary capillary bed.
  - The blood leaving the left ventricle becomes further desaturated when mixed with blood entering the aorta through the ductus arteriosus, having bypassed gas exchange in the lungs.
  - With blood distal to the ductal entrance to the aorta being more desaturated than the pre-ductal blood, the oxyhemoglobin saturation measured by pulse oximetry or arterial blood gas (ABG) in the right arm may be higher than in the left arm or legs.
  - This is known as differential oxyhemoglobin saturation or differential cyanosis.
- Newborn screening for CCHD.
  - The American Academy of Pediatrics recommends screening by pulse oximetry before discharge from the newborn nursery to ascertain presence of CCHD.
  - By 24 hours of life, an oxyhemoglobin saturation <95% is not normal and is supportive of a cyanotic or mixing cardiac lesion.

LABORATORY EVALUATION

- To most observers, cyanosis becomes visible when the concentration of deoxygenated hemoglobin approaches 3–5 g/dL; some reports suggest the threshold may be as low as 1.5 g/dL.
- Cyanosis in a patient with a hemoglobin concentration of 15 g/dL will be apparent at an SaO_2 somewhere between 70% and 80%.
  - 5 g/dL of hemoglobin is desaturated at 70% SaO_2.
  - 3 g/dL is desaturated at 80% SaO_2.
- The higher the patient's hemoglobin concentration, the more evident the cyanosis.
  - For example, 5 g/dL represents one-half of the hemoglobin in a child with 10 g/dL but only one-third in a patient with 15 g/dL of hemoglobin.
  - As hemoglobin concentration falls, cyanosis becomes apparent only at lower oxyhemoglobin saturations.
- Because hemoglobin concentration varies in healthy and ill children and throughout life, cyanosis appears at different degrees of desaturation in different children and at different times.

- Progressively anemic patients do not manifest cyanosis until oxygen saturations have fallen substantially.
- A patient who is polycythemic with a hemoglobin concentration of 20 g/dL might manifest cyanosis when 92% saturated (1.5 g/dL desaturated hemoglobin) and certainly when 75% saturated (5 g/dL desaturated hemoglobin).
- SpO_2 and SaO_2 (often used interchangeably).
  - SpO_2: arterial hemoglobin oxygen saturation measured with a pulse oximeter
  - SaO_2: saturation measurement obtained from ABG
  - Usually almost identical in the absence of significant amounts of carbon monoxide, methemoglobinemia, elevated bilirubin levels, or very poor perfusion
- Pulse oximetry.
  - Measures SaO_2 directly.
  - Permits recognition of decreasing degrees of SaO_2 before cyanosis is visible.
  - Screening newborns using pulse oximetry detects hemoglobin desaturation indicative of congenital heart disease that may not be obvious on examination.
- ABG sampling.
  - Measures pH, PCO_2, PO_2, and SaO_2.
  - Depending on the analyzer, SaO_2 is measured directly in a process called co-oximetry or is calculated based on the pH, PCO_2, PO_2, and oxyhemoglobin dissociation curve.
- Pulmonary versus cardiac cyanosis.
  - Immediately obtain pulse oximetry with any suggestion of cyanosis.
  - Early in life, PaO_2 may increase to >100 mm Hg in neonates with cyanotic heart disease with high pulmonary blood flow (eg, total anomalous pulmonary venous return).
- CCHD.
  - Simultaneous upper- and lower-extremity pulse oximetry measurements can be diagnostic.
  - Differential cyanosis.
    - SaO_2 higher in right arm than in umbilical artery or lower extremities indicates that venous blood has been added to the aorta at the level of the ductus arteriosus.
  - Reverse differential cyanosis.
    - With d-TGA in the presence of pulmonary hypertension or coarctation of the aorta, saturation in the right arm is less than in lower extremities because oxygenated blood is added to desaturated blood at the level of the PDA.
- Cyanosis with dyshemoglobinemia.
  - Standard pulse oximeters do not accurately measure SaO_2 in the presence of carbon monoxide; special pulse oximeters are available to determine carboxyhemoglobin saturation.
- Cyanosis in the newborn.
  - A newborn should have oxyhemoglobin saturation measured in the right arm and in one leg at 24 hours of life.
  - Hyperoxia test
    - May help distinguish hypoxemia for respiratory reasons (pneumonia or neonatal respiratory distress syndrome) from CCHD or PPHN.
    - Perform in newborns with cyanosis, oxyhemoglobin desaturation, or low PaO_2 to determine whether problem is pulmonary oxygenation, from an anatomic shunting of blood through the PDA, or an intracardiac lesion.
    - In pulmonary cyanosis or hypoxemia, SaO_2 and PaO_2 should substantially increase with administration of 100% oxygen.
    - PaO_2 <100 mm Hg in an enriched-oxygen environment is a strong indicator of CCHD or PPHN.
    - With a heart lesion in which some pulmonary blood flow is present, PaO_2 or SaO_2 can increase substantially during a hyperoxia test.
    - PaO_2 >250 mm Hg makes cyanotic heart disease unlikely, but PaO_2 of 100–250 mm Hg warrants further investigation.
    - When performing a hyperoxia test, simultaneously determine pre- and post-ductal SaO_2 or PaO_2 to delineate the presence of a shunting pattern.

IMAGING

- Pulmonary versus cardiac cyanosis
  - With inadequate rise in PaO_2 or oxygen saturation from a hyperoxia test, perform echocardiography immediately to ascertain the presence or absence of a congenital heart lesion.
  - In general, perform echocardiography to assess for the possible presence of CCHD whenever hypoxemia is not responsive to supplemental oxygen or mechanical ventilatory support.
- TOF
  - Chest radiographs reveal
    - Normal cardiac size
    - Rounded, uplifted apex
    - Concavity at the site of the pulmonary artery

  - "Boot-shaped" heart
  - Diminished pulmonary vasculature
- Electrocardiogram demonstrates
  - Right axis deviation
  - Eight ventricular hypertrophy

- Ebstein anomaly of the tricuspid valve
  - Newborns may have massive cardiomegaly on chest radiograph.
- TGA
  - Chest radiograph of neonate with TGA and intact intraventricular septum
    - Narrowed superior mediastinum with an egg-shaped cardiac silhouette (egg on a string)
    - Mild cardiomegaly
    - Increased pulmonary vascular markings
- Truncus arteriosus
  - Radiographs usually show cardiomegaly.
- Total anomalous pulmonary venous return
  - Radiographs show pulmonary congestion in the absence of enlarged cardiac silhouette.
- Cyanosis in the newborn
  - With gradient in saturation or saturation ≤95%, obtain echocardiogram before discharge from the hospital.
  - PaO_2 <100 mm Hg in an enriched-oxygen environment is a strong indicator of CCHD or PPHN.
    - Obtain an echocardiogram to evaluate for congenital heart disease.
- Croup
  - Airway radiographs may reveal subglottic narrowing.
- Aspiration of foreign body
  - Many foreign bodies are not radiopaque, warranting high index of suspicion regardless of findings.

SPECIFIC TREATMENT

- Acrocyanosis
  - Warming the patient rapidly resolves cyanosis caused by moderate cold exposure.
- TOF
  - Acute tet spell
    - Put the patient in a knee-to-chest position to increase systemic vascular resistance.
    - Administer supplemental oxygen, sedation, and a β-blocker.
    - Ultimately, only surgical repair can provide consistent pulmonary blood flow.
    - With sufficient pulmonary blood flow from collateral vessels from the descending aorta (identified by a continuous murmur heard over the back), the patient may not require treatment with prostaglandin E_1 (PGE_1) to maintain a PDA.
- Ebstein anomaly of the tricuspid valve
  - Infants with severe disease require PGE_1 to maintain pulmonary blood flow until pulmonary vascular resistance has fallen and adequacy of the right ventricle and pulmonary valve can be assessed.
- TGA
  - These newborns often receive PGE_1 until the atrial communication through the foramen ovale can be enlarged by balloon atrial septostomy.
  - Surgical repair, typically by arterial switch operation, is often undertaken in the first week of life.

WHEN TO REFER

- Cyanosis in the newborn
  - If desaturation is present and if saturation does not improve with administration of 100% oxygen, consult a neonatologist or pediatric cardiologist.

Cystic and Solid Masses of the Face and Neck

DEFINITION

- Cystic lesions are congenital cysts or vascular malformations.
  - Traumatic hematomas and abscesses may appear to be cystic.
- Solid neck masses usually consist of inflammatory lymph nodes or, rarely, neoplastic lesions.

SIGNS AND SYMPTOMS

History

- The physician should determine
  - Whether the neck mass was observed at birth
    - Lymph nodes >1 cm rarely appear at birth, whereas many congenital cysts are noted in the newborn period.
    - Some congenital cysts may not be noted until childhood or beyond and are detected only when they become infected.
  - Whether it has increased or decreased in size
  - Whether it has changed color
  - Whether the lesion has drained or opened
- Any history of pain or tenderness is important.
  - Congenital cysts are non-tender unless they become infected.
  - Inflamed lymph nodes are tender and painful.
  - Pain during eating suggests parotid gland involvement.
- Infectious processes and cancer may be suggested by
  - History of fever
  - Other systemic symptoms, such as loss of appetite, weight, and fatigue

Physical Examination

- The first step in the physical examination is to determine whether abnormalities exist in other parts of the body.
  - Other cysts
  - Lymphadenopathy
  - Hepatosplenomegaly
  - Skin lesions
  - Signs of infection
- The exact anatomic location of the neck mass must be determined.
  - Midline masses usually are associated with a thyroid abnormality.
  - A mass along the anterior edge of the sternocleidomastoid muscle that moves with swallowing or that has a sinus opening to the surface of the overlying skin is likely to be a branchial cleft cyst.
  - The clinician should note whether the mass is in a typical location of a lymph node.
- Characteristics of the mass must be determined.
  - Consistency, color, and firmness
  - Presence of tenderness
  - Size
  - Whether the mass moves or is fixed
    - Masses that move with swallowing or with tongue protrusion suggest a thyroglossal duct cyst.
      - These lesions may be tethered to the foramen cecum by the thyroglossal duct remnant.
    - Both cysts and benign lymph nodes are freely mobile.
    - Malignant lesions are more likely to be fixed to underlying structures.
- Neoplasms may be suspected.
  - Rapidly growing, painless neck masses are worrisome because they may be neoplastic.
  - Additional signs associated with a neoplastic process include
    - Fixation of the mass to subcutaneous tissue.
    - Firm consistency.
    - Size >3 cm.
    - Presence of constitutional symptoms.
    - Supraclavicular nodes are the most likely neck mass to be malignant and should always be investigated.

DIFFERENTIAL DIAGNOSIS

- Major challenges in the differential diagnosis are
  - Differentiating congenital masses from lymph nodes
  - Determining the type of congenital lesion
- Most neck masses encountered by pediatricians are lymph nodes, not cysts.
- Knowing the location of the different groups of lymph nodes within the anterior and posterior anatomic triangles of the neck is crucial.

Congenital Cysts

Thyroglossal Duct Cysts

- Account for >70% of congenital cysts of the neck.
- Are not often detected at birth but usually are noted first after 2 years of age.
- May show initially as an inflamed, tender mass.
- When not infected, they are smooth, firm, mobile, and non-tender and move upward with tongue protrusion or swallowing.

- Differential diagnosis includes
  - Sebaceous cysts
  - Epidermal cysts
  - Submandibular lymph nodes
  - Lipomas

Branchial Cleft Cysts

- Account for >20% of congenital cysts of the neck.
- Most branchial cleft cysts arise from the second cleft or pharyngeal pouch.
- They appear as a small dimple or opening anterior to the middle portion of the sternocleidomastoid muscle.
- The cyst, located just under the skin, is non-tender, firm, and mobile.
- A small sinus, which occasionally drains fluid to the surface of the overlying skin, may be present; a long fistulous tract may extend from it to the tonsil bed.
- Branchial cleft cysts without sinuses often are unnoticed until later childhood when they become infected.
- Infected cysts can easily be confused with lymphadenitis.

Vascular Malformations and Other Lesions

- Account for 4%–5% of congenital cysts of the neck

Other Lesions

- Other lesions included in the differential diagnosis are
  - Sternocleidomastoid muscle masses associated with torticollis
  - Small cystic hygromas
  - Epidermoid cysts
  - Neurofibromas
  - Lipomas
  - Ectopic thyroid gland
- Other congenital masses occur rarely in the head and neck.

Lymphatic Malformations

- Congenital, avascular masses derived from congenital obstruction of lymphatic vessels.
- Usually multilocular, fluid-filled, soft, compressible, painless masses located in the posterior triangle just behind the sternocleidomastoid muscle and in the supraclavicular fossa.
- Occur infrequently in the axilla, on the trunk, or on the extremities.
- In older children, when they occur within the subcutaneous tissues, they may be mistaken for a lipoma or hemangioma.
- Usually can be transilluminated.
- May grow rapidly because of accumulation of lymph.
  - Can reach an enormous size, compressing important structures and obstructing the airway
- Although diagnosis usually is obvious during the physical examination, smaller lymphatic malformations may resemble hemangiomas or other cysts.

Epidermoid Cysts

- Relatively common masses that may arise from an embryologic or fusional defect.
- Usually located at midline on the face, most often at the level of the eyebrows.
- These small cysts feel doughy and smooth and contain sebaceous material, sometimes even hair, cartilage, or bone.
- One-third are present at birth; the remaining two-thirds appear by school age.

Preauricular Cysts and Sinuses

- The most common anomalies arising from an embryologic fusion failure of precursor tissues that develop into the external ear.
- The sinuses are pinhole-sized pits.
  - Usually located anterior to the helix
  - May contain a short sinus tract
- Preauricular cysts often are bilateral.
- They are inherited in an autosomal-dominant manner with incomplete penetrance and are found more commonly in blacks than in whites.
- They are a far more common cause of preauricular lesions than are first branchial cleft cysts and sinuses, which are located in the same area.
- Hearing deficit may be associated with these lesions, but their prevalence is unknown.

Deep Hemangiomas

- Hemangiomas are vascular lesions within the subcutaneous tissues that may appear in any part of the body and may be difficult to differentiate from congenital cysts.
- They are less firm, more diffuse, and more easily compressible than cystic masses (except for lymphatic malformations).
- Unlike lymphatic malformations, deep hemangiomas do not transilluminate, and the skin overlying these vascular lesions is often bluish.
- They often begin to increase in size during the first few months of life but usually regress spontaneously by school age.

- For masses that compress vital structures or have the potential to cause severe disfigurement, oral propranolol can be used to hasten involution.

Solid Neck Masses

- Cervical lymph nodes
  - Often palpable in normal children.
  - Can be distinguished by location, size, shape, consistency, and mobility.
  - Enlarged cervical lymph nodes (>1 cm) should be defined further by
    - Association with surrounding nodes or generalized adenopathy
    - The presence of an infection of the head or pharynx
    - Localized signs of inflammation and erythema
  - Cervical adenitis typically develops as a swollen, tender, erythematous mass in a child with fever.
    - *Staphylococcus aureus* and *Streptococcus pyogenes* account for 80% of acute unilateral cervical adenitis and usually respond to oral antibiotics, such as a penicillin or cephalosporin.
  - Chronic inflammation of the lymph nodes can be seen with infections such as cat-scratch disease, atypical mycobacterium, and toxoplasmosis.
- Cancer
  - Malignant tumors often are found as a single supraclavicular mass or as multiple or matted masses crossing into the anterior and posterior triangles.
  - >25% of children with cancer have a tumor of the head or neck.
  - The most common neck cancers include
    - Hodgkin and non-Hodgkin lymphoma
    - Lymphosarcoma
    - Rhabdomyosarcoma
    - Fibrosarcoma
    - Thyroid tumors
    - Neuroblastoma

DIAGNOSTIC APPROACH

- Because the causes of neck masses range widely from common inflamed lymph nodes and cysts to rare neoplasms, an orderly approach to the workup and management of a neck mass is needed.
  - The mass must be defined as lateral or midline.
  - The exact anatomic position of the mass must be determined.
  - Localizing a lateral neck mass further into the anterior cervical triangle (anterior to the sternocleidomastoid muscle) or the posterior cervical triangle is helpful.

LABORATORY FINDINGS

- A complete blood cell count and blood culture can sometimes be helpful in assessing a tender, erythematous mass.
- Erythrocyte sedimentation rate may be helpful in differentiating inflammatory or malignant lesions from other lesions, such as cysts.
- Thyroid hormone should be measured if the thyroid gland is enlarged.

IMAGING

- Ultrasonography or magnetic resonance imaging can determine whether the mass is cystic or solid or whether it extends to deeper structures within the neck.
- Thyroglossal duct cysts.
  - Unless normal thyroid tissue is palpable, the presence of the thyroid gland should be confirmed by ultrasonography or technetium scan.
    - What may seem to be a thyroglossal duct cyst may actually be an ectopic thyroid gland; removal would leave the child dependent on thyroid hormone supplementation for life.
- Cystic hygromas.
  - Ultrasonography reveals fluid and multiple cystic components, confirming the diagnosis.

DIAGNOSTIC PROCEDURES

- Biopsy (needle or excision) of the lesion may be necessary to establish the diagnosis, especially when a malignant lesion is being considered.

TREATMENT APPROACH

- For children with enlarged cervical lymph nodes and evidence of infection, antibiotic therapy is recommended.
  - The child should be evaluated further and monitored closely until the enlarged node has resolved if
    - Adenopathy is persistent.
    - Inflammation is not present.
    - Any characteristics are worrisome (eg, the node is >3 cm, immobile, associated with systemic symptoms, in an abnormal location).

- Congenital cysts and masses
  - Should be monitored closely by the primary care physician.
  - Acute bacterial infections should be treated with systemic antibiotics.
  - Thyroglossal duct cysts, branchial cleft cysts, cystic hygromas, and epidermal cysts should be referred to a surgeon who is experienced at excising these congenital lesions.
  - Elective surgery before an infection develops is preferable because excision of an entire sinus tract, fistula, or embryologic connection is more difficult after an infection.
  - However, many primary care physicians and surgeons prefer to delay surgery until the infant is beyond infancy and can better tolerate the procedure.
- Hemangiomas can be observed without referral unless they begin to impinge on vital structures.
  - Hemangiomas that interfere with physiologic functions (eg, blocking vision, interfering with eating) may be
    - — Treated with glucocorticoid steroids
    - — Referred to a surgeon for management

SPECIFIC TREATMENTS

- Thyroglossal duct cysts
  - Because the likelihood of infection is high, thyroglossal duct cysts should be removed surgically.
- Cystic hygromas
  - Because spontaneous regression is rare and the risk of compression of vital upper airway structures is high, surgical removal is indicated.
  - Several procedures often are necessary to remove large lesions completely.
- Cavernous hemangioma
  - Surgery is indicated only for masses that compress vital structures or that cause severe disfigurement.
- Epidermoid cysts
  - Because these cysts may become infected and may form deep tracts, surgical excision is indicated.
- Cervical lymph nodes
  - Lymph node aspiration usually is reserved for patients whose disease does not respond to initial therapy.
  - Incision and drainage may be needed for masses that become fluctuant.

WHEN TO ADMIT

- Infected mass that is unresponsive to oral antibiotics
- Worrisome mass requiring immediate intervention and imaging
- Mass that compromises the airway or other vital structures

WHEN TO REFER

- Congenital cysts or tracts
  - All congenital cysts or tracts should be removed.
- Mass that does not resolve with antibiotic therapy (≥2 weeks)
- Mass in the thyroid gland
- Mass in the parotid gland
- Rapidly enlarging mass (>3 cm)
- Mass that is fixed or lymph nodes that are matted
- Mass in an area that causes concern (eg, supraclavicular)
- Abnormal chest radiograph
- Systemic signs and symptoms (eg, fever, weight loss, easy fatigability, hepatosplenomegaly)

FOLLOW-UP

- All cystic and solid masses of the neck require close follow-up to make sure they are not enlarging rapidly and interfering with physiologic functions, such as vision, eating, and speaking.

COMPLICATIONS

- Interference with physiologic functions, such as vision, eating, or speaking
- Compromise of vital structures, such as airways or the carotid artery

PROGNOSIS

- For children with enlarged cervical lymph nodes and evidence of infection
  - Antibiotic therapy should improve the condition within 7 days.
  - The condition should resolve completely over the next few weeks.
- Cystic lesions have a good prognosis after surgical removal.
- Prognosis for malignant diseases depends on the type of disease and extent of spread.

DEFINITION

- Cystic fibrosis (CF) is an autosomal-recessive disease.
  - Involves exocrine and endocrine gland dysfunction
  - Involves multiple organ systems, especially the pancreas and lungs

SIGNS AND SYMPTOMS

Presenting Symptoms

- Patients with CF most commonly have respiratory symptoms.
- Recurrent pulmonary infections in 49% of patients at presentation.
- Failure to thrive or malnutrition in 40%.
- Steatorrhea or abnormal stools in 32%.
- Meconium ileus or intestinal obstruction in 10%.
- Family history of CF in 15%.

Pulmonary

- The common pulmonary symptoms at presentation include
  - Recurrent cough (most common) that is productive of purulent sputum
    - Cough may initially be dry but becomes progressively productive of purulent sputum.
    - Over-the-counter therapies are generally ineffective.
    - Antibiotic treatment produces only transient, partial improvement.
    - The cough is present day and night and may be exacerbated by physical activity or by crying in infants.
  - Difficult-to-control wheezing
    - Some children with CF also have asthma.
  - Nasal polyps
  - Recurrent otitis media
  - Sinusitis
  - Pneumonia
- Vitamin deficiency, specifically deficiencies in the fat-soluble vitamins A, D, E, and K
- Other manifestations of CF that may trigger initial patient encounters include
  - Salt depletion syndrome.
  - Nasal polyps.
  - Hepatobiliary disease.
  - Impaired fertility.
  - Failure to thrive.
  - Irritability.
  - Vomiting.
  - Salt crystals are sometimes caked on the skin.

Gastrointestinal

- In the pancreas, abnormal electrolyte secretion from the epithelial cells lining the pancreatic ducts results in
  - Dehydration of the ductal secretions.
  - Blockage of pancreatic ducts.
  - Destruction of the pancreatic acini.
    - Pancreatic enzyme secretion is significantly decreased.
  - Bicarbonate secretion from the pancreatic ducts is also reduced.
    - In 85%–90% of patients with CF, this further decreases the effectiveness of the pancreatic enzymes, known as *pancreatic insufficiency* (PI).
  - PI results in the malabsorption of
    - Fat
    - Proteins
    - Carbohydrates
    - The fat-soluble vitamins A, D, E, and K
  - Children with PI have difficulty growing and gaining weight.
  - Optimization of nutritional status is also essential to maintaining pulmonary function.
- Patients with PI are at risk for intestinal dysfunction.
  - 20% of newborns with CF have meconium ileus.
    - Obstruction of the distal ileum with thick, inspissated, poorly hydrated material
  - Clinically, newborns exhibit
    - Delayed passage of meconium
    - Abdominal distention
    - A bubbly or granular-appearing material in the region of the terminal ileum on radiography
  - In older children and adults partial or complete obstruction of the small or large intestine may be caused by
    - Poor hydration of intestinal contents
    - Decreased secretion of pancreatic enzymes
    - Inspissated intestinal secretions
    - Fecal stasis
    - Distal intestinal obstruction syndrome (DIOS) may develop as an acute event or may occur chronically, with the following symptoms:
      - Vomiting.
      - Abdominal distention.
      - Crampy abdominal pain.
      - Possibly a mass in the abdomen, most often in the right lower quadrant.
      - Patients may continue to pass stool around a partial obstruction.

- Regions of stool retention may serve as lead points for intussusception.
- Some patients experience rectal prolapse secondary to difficulty passing stool and from increased intra-abdominal pressure from coughing.

- Symptomatic liver disease is an uncommon manifestation of CF, with characteristic pathologic findings of
  - Focal biliary cirrhosis with edema
  - Chronic inflammatory cell infiltration
  - Bile duct proliferation with patchy accumulation of eosinophilic material in the intrahepatic ducts
- The localization of *CFTR* to the apical membrane of the intrahepatic bile duct cells suggests that a reduction in *CFTR* activity in CF may result in dehydration and increased viscosity of the bile.
  - May be a key factor in the pathophysiological features of the hepatic disease.
  - Prolonged jaundice can occur in neonates.
  - Some patients may develop fatty infiltration of the liver.
  - The characteristic liver lesion in CF is focal or multilobular cirrhosis.
    - Hepatomegaly is detected on examination.
    - The secondary development of splenomegaly suggests the possibility of portal hypertension.
    - Other features of portal hypertension, such as variceal bleeding, have been reported in CF but are relatively rare.

DIFFERENTIAL DIAGNOSIS

- The differential diagnosis includes
  - Asthma
  - Environmental allergies
  - Immunodeficiency syndromes
  - Ciliary agenesis or dyskinesia
  - α_1-Antitrypsin deficiency
  - Foreign body aspiration

DIAGNOSTIC APPROACH

General

- In most cases, no known family history of CF is found.
- Parents often report that their child has had
  - Recurrent pneumonia.
  - Sinusitis.
  - Bronchitis.
  - Otitis media.
  - Pneumonia and atelectasis may have occurred repeatedly in the same area of the lung.
  - A history of nasal polyps without a concomitant history of nasal allergies.
  - Changes to the child's nail beds consistent with clubbing.
- From the gastrointestinal standpoint, infants with CF are often voracious feeders despite having poor weight gain.
  - The infants' stools are frequent, bulky, loose, and foul-smelling.
    - Stools are so voluminous that they may overflow the diaper.
  - Grease may be seen in the stool, absorbed in the diaper, or, in the case of older children, seen in the toilet bowl.
  - Abdominal cramping and bloating after eating are common.
  - Foul-smelling flatulence may be described.
- Test for CF.
  - Any neonate born with meconium ileus with delayed passage of meconium
  - Any infant or child with rectal prolapse

Vital Signs

- Respiratory rates and heart rates should be monitored relative to age-appropriate normal values. Fever and exacerbation or progression of the underlying lung disease may elevate both values.
- Oxygen saturation should be assessed at each visit.
- Overnight pulse oximetry or polysomnography should be considered to evaluate for nocturnal hypoxemia and hypercarbia in patients with more advanced disease.

Growth Parameters

- At all ages, pay particular attention to growth parameters.
  - Weight, height, head circumference, and weight for length in children ≤2 years.
  - Weight, height, and body mass index in children >2 years.
  - The child's height percentile should be compared with the height percentile predicted from the parental height.
- Concern should arise whenever a child
  - Fails to gain weight
  - Loses weight
  - Crosses percentiles for height or weight

Head and Neck

- Otoscopic examination should be performed at all visits to assess for otitis media.
- Audiometry should periodically be performed if a child has recurrent otitis media or is exposed to frequent doses of aminoglycosides.
- Nasal mucosa should be inspected for discharge, swelling of the tissue, or polypoid tissue.
- Palpation of the sinuses should be performed.
- Examination of the oropharynx should include assessment of the tonsils and the posterior pharynx.
  - Children with CF have similar risk for adenotonsillar hypertrophy as children without CF.
- The posterior pharynx should be checked for exudates emanating from the nasopharynx.

Chest and Lungs

- Coughing frequency and the productivity of the cough should be assessed.
- The child's ability to communicate without coughing, becoming dyspneic, and using accessory muscles is indicative of the status of the lung disease.
- Auscultation of the lungs may reveal clear breath sounds.
  - With exacerbation of the underlying lung disease, wheezing, rhonchi, or crackles may be heard.
  - As the patient's pulmonary status worsens, these findings may not change with antibiotic therapy.
    - Any clearing that does occur may be short lived.
- As the lung disease progresses, breath sounds may become globally decreased.
- Tubular breath sounds may be heard in areas of severe tissue destruction or bronchiectasis and fibrosis.
- Unilaterally decreased breath sounds should raise concern about development of pneumothorax, particularly in association with an acute onset of dyspnea.
- Progression of the obstructive component of CF lung disease is increasing hyperinflation of the lungs.
  - The chest may take on a barrel shape with an increased anterior–posterior diameter.
- Progression of the fibrotic component of the lung disease results in tachypnea and decreased vital capacity.

Heart

- Fixed splitting of the first and second heart sounds, with increased loudness of the second heart sound, may be heard with progression of the lung disease and development of cor pulmonale.

Abdomen

- Infants often have protuberant abdomens.
  - Distention of the abdomen with pain on palpation may be noted in children with acute intestinal obstructions.
- The frequency and distribution of bowel sounds should be assessed by auscultation.
- Palpation should be performed to assess for
  - Retention of stool, most commonly in the left lower quadrant
  - Tenderness
  - Hepatomegaly
  - Splenomegaly

Genitourinary Tract

- Tanner staging should be performed
  - By direct inspection
  - By having the child indicate his or her developmental status from a series of pictures
- Girls should be questioned about
  - Onset of menstruation
  - Regularity of cycles
  - Associated symptoms
- All sexually active girls should undergo annual pelvic examination.

Extremities

- Joints should be examined for swelling that may be caused by CF-related arthropathy.
- The digits and nail beds should be examined for clubbing and cyanosis.
- Edema may arise from hypoproteinemia, especially in
  - Newly diagnosed malnourished infants
  - Patients with end-stage lung disease
  - Patients with cor pulmonale

LABORATORY FINDINGS

General

- Laboratory tests
  - Increased
    - Serum pH
    - Bicarbonate levels
  - Decreased serum levels of
    - Sodium
    - Chloride
    - Potassium

- Diagnosis of CF requires
  - Either 2 positive sweat tests *or*
  - Genotype analysis revealing 2 *CFTR* mutations known to cause CF
  - Plus one of the following symptoms:
    - Chronic sinopulmonary disease
    - Gastrointestinal or nutritional abnormalities
    - Obstructive azoospermia in boys
    - Salt depletion syndrome
    - CF in a first-degree relative

Sweat Testing

- The pilocarpine iontophoresis technique of Gibson and Cooke is the gold standard for the diagnosis of CF.
  - Pilocarpine stimulates the secretion of sweat.
  - The volume of sweat and concentration of chloride secreted are then measured.
  - Sweat testing should be performed in accordance with the Clinical and Laboratory Standards Institute guidelines.
- Normative sweat chloride values are age dependent.
  - Infants ≤6 months
    - Reference chloride values are ≤29 mEq/L.
    - Values of 30–59 mEq/L are borderline, and repeat sweat or genetic testing should be performed.
    - Values ≥60 mEq/L are indicative of CF.
  - Patients >6 months
    - Reference chloride values are <40 mEq/L.
    - Values of 40–60 mEq/L are considered borderline.
    - Chloride values >60 mEq/L are considered diagnostic of CF.
- Repeat sweat or genetic testing is required to make a definitive diagnosis.
- For some borderline cases, referral to specialized care centers may be needed to confirm or rule out CF.
  - For example, a borderline sweat test result with identification of only 1 *CFTR* mutation.
  - Assess *CFTR* function by measuring nasal potential difference.
  - Abnormal results on 2 nasal potential difference tests are indicative of CF.
- There are many possible causes of false-positive sweat test results.
  - Laboratory error.
  - Untreated adrenal insufficiency.
  - Autonomic dysfunction.
  - Ectodermal dysplasia.
  - Glucose-6-phosphate deficiency.
  - Hypothyroidism.
  - Malnutrition.
  - Mucopolysaccharidosis.
  - Glycogen storage disease (type 1).
  - Fucosidosis.
  - Hereditary nephrogenic diabetes insipidus.
  - Mauriac syndrome.
  - Pseudohypoaldosteronism.
  - Familial cholestasis.
  - A repeat confirmatory sweat test should be performed together with genetic mutation analysis.
  - Sweat testing should not be performed <48 hours of age.
  - False-negative values can result from edema, malnutrition, and laboratory error.
  - Several *CFTR* mutations that cause CF can also result in a false-negative sweat test result.
  - When genetic testing is done to resolve borderline sweat testing or when genetic testing alone is performed
    - The presence of 2 mutations known to cause CF is required to make the diagnosis.
    - DNA from blood or buccal swabs can be used for genetic testing.

Newborn Screening

- Newborn screening for CF has been universally adopted in the United States.
  - Evidence of moderate benefits and low risk of harm are justification for screening.
  - Evidence exists to support the efficacy of newborn screening in the areas of
    - Improved nutritional status
    - Cognitive development
    - Economic benefit
    - Improved survival
  - Effect of newborn screening on pulmonary status varies.
  - Benefit of improved height and weight status on pulmonary status is well known.
    - Believed to outweigh variability in data concerning pulmonary outcomes for newborn screening
- Newborn screening for CF is typically a 2-tier test.
  - The first tier involves measuring serum immunoreactive trypsinogen (IRT) levels.
    - IRT values are elevated in newborns with CF.
      - False-negative results may occur, particularly in newborns with meconium ileus.
      - All newborns with meconium ileus should undergo sweat or genetic testing.

- The second tier of testing varies among states.
  - — May use repeat IRT measurement or limited genetic mutation analysis.
  - — Sweat to confirm results of newborn screening.
- If the newborn has signs and symptoms consistent with CF, sweat or genetic testing should be performed regardless of newborn screening results.

Microbiological Assessment

- Cultures to assess lower respiratory tract flora should be obtained initially 1 week after diagnosis or at 1 month of age and then at 3, 6, and 12 months of age.
- After 1 year of age, clinically stable patients should undergo respiratory tract culture at least quarterly and whenever there is any change in clinical status.
  - A mycobacterial culture should be obtained before starting azithromycin and periodically thereafter and when there is any change in clinical status.
    - — Expectorated sputum sample is the usual source.
    - — Throat or cough swab is often obtained in newborns, infants, and young children who cannot expectorate; not necessarily predictive of lower-airway pathogens.
- In young children, *Staphylococcus aureus* and *Haemophilus influenzae* are the most common organisms.
- With advancing age, *Pseudomonas aeruginosa* becomes the predominant pathogen.
- Other pathogens can also infect the lungs in CF.
  - *Burkholderia cepacia* complex.
  - *Stenotrophomonas maltophilia.*
  - The prevalence of methicillin-resistant *S aureus* has been increasing over the past decade.
- Specialized media are recommended to ensure isolation of pathogens.
  - *P aeruginosa* is best detected using MacConkey agar.
  - *S aureus* on mannitol salt agar or Columbia colistin–nalidixic acid agar.
  - *H influenzae* on horse blood or chocolate agar.
  - *B cepacia* complex is best determined using *B cepacia*–selective agar, oxidation-fermentation polymyxin bacitracin lactose agar, or *Pseudomonas cepacia* agar.
- Antimicrobial susceptibility testing should be determined using an agar-based diffusion assay.
  - Use E-tests (antibiotic-impregnated strips) or antibiotic discs rather than automated commercial systems.
  - Organisms in the *B cepacia* complex and other unidentified gram-negative rods should be further evaluated at a reference laboratory.
    - — For instance, Cystic Fibrosis Foundation–sponsored *B cepacia* laboratory at the University of Michigan

IMAGING

- Chest radiography should be performed on infants and children initially between 2 and 6 months of age, at 1–2 years of age, and then every 2–4 years in clinically stable patients.
  - Annually in patients with declining pulmonary function.
  - As clinically indicated at times of pulmonary exacerbation in all patients.
  - Bronchial wall thickening, together with hyperinflation caused by small-airway obstruction, is the first change noted.
    - — Bronchiectasis develops with time.
    - — Acute or chronic infiltrates may be noted depending on the patient's clinical status.
    - — Progression of radiographic changes varies among patients and may be more sensitive than changes in pulmonary function tests.
- Examine lateral chest radiographs for fractures at least annually in patients ≥8 years and at risk for bone disease because they are
  - Malnourished
  - Have severe pulmonary disease
  - On chronic glucocorticoid therapy
  - Have delayed puberty
  - Have low levels of 25-hydroxy vitamin D
- Children with these risk factors for bone disease who are ≥8 years should undergo a dual-radiograph absorptiometric scan to measure bone density.
- All children and adolescents with CF should have bone densitometry performed by their 18th birthday.
- Chest computed tomography (CT) may detect structural changes in the lung before symptoms are present.
  - Enthusiasm for periodic chest CT has been limited by concerns about radiation exposure.
  - No current formal recommendations.
- Abdominal ultrasonography should be performed
  - If liver function test results change

- If hepatomegaly or splenomegaly is detected
- Fetal ultrasonography may reveal hyperechoic bowel.
  - Intestinal manifestations of CF may be present even before birth.
  - Suggests retention of mucus material in the intestine.
- In older patients, as in meconium ileus, bubbly, granular material can be detected by radiography in the region of intestinal obstruction.

DIAGNOSTIC PROCEDURES

- Bronchoscopic studies of infants with CF reveal that neutrophil and proinflammatory (interleukin-8) mediator levels are increased even though patients appear clinically well.
- Spirometry should be performed every 3–6 months and as needed on the basis of the patient's pulmonary status.
  - Most children <6 years cannot perform the test reliably.
    - Infant pulmonary function testing is available at many CF care centers.
  - It may be difficult to get a reliable, reproducible effort, especially when the child is first learning to perform the test.
  - Best performed with supervision of a certified respiratory therapist trained to work with children.
  - Changes seen in pulmonary function are obstructive in nature secondary to plugging of the small airways with thick secretions.
  - Severity of pulmonary disease is categorized on the basis of percentage predicted forced expiratory volume in 1 second (FEV_1).
    - Reference lung function is defined as an FEV_1 >90%.
    - Mild lung disease is 70%–89%.
    - Moderate disease is 40%–69%.
    - Severe disease is <40%.
  - <20% of children have moderate to severe lung disease.
  - One measure of the health of the small airways is a forced expiratory flow of 25%–75% of vital capacity.
    - The average amount of air expelled over the middle half of all the air expelled during spirometry.
    - Clinicians should consider this value, particularly in younger children.
    - Researchers have suggested that changes may be seen in a forced expiratory flow of 25%–75% before FEV_1.

TREATMENT APPROACH

- Improved survival for patients with CF seen over recent decades is likely to continue.
  - Greater understanding of the pathological characteristics of the disease
  - Significant increase in therapeutic options
- The challenge to the practitioner is in choosing the best combination of therapies for the individual patient to maintain optimal health status.
- Consultation with a regional CF care center and physicians who are experienced with the nuances of CF care is strongly recommended.
- More specific therapies aimed at the basic defect in CF are being developed.
- All children with diagnosed CF and those who have clinical stigmata of CF but equivocal diagnostic test results should be referred to a local CF care center.
- A team of individuals that can provide counseling, support, and education to families of newly diagnosed children comprises
  - Pediatrician, most often a pediatric pulmonologist
  - Nurse
  - Respiratory therapist
  - Dietitian
  - Social worker
- Pulmonary and gastrointestinal therapies can be initiated.
- Newborns and infants
  - Should be seen monthly for the first year of life and every 2–3 months during the second year.
    - Facilitate ongoing family education.
    - Ensure adequate growth and nutrition for the child.
    - Adjust or initiate therapies as needed.
- Children
  - Should be seen at least quarterly in the CF care center.
- CF social workers are an invaluable resource for families.
  - Help families deal with the psychological and financial aspects of raising a child with CF.
  - Work with the child to help him or her develop into an adult capable of managing the disease independently.
- CF care centers also can make clinical trials of novel therapies available to patients.
  - The CF care center should not be considered a replacement for the general pediatrician.

- The child must continue to receive routine well-child care.
- CF care centers generally have physicians available at all times to consult on medical management issues relating to CF.
- A list of accredited CF care centers in the United States can be accessed at www.cff.org.

SPECIFIC TREATMENTS

Pulmonary Therapy

- The Cystic Fibrosis Foundation has developed a series of guidelines related to
  - Airway clearance
  - Chronic medications
  - Management of pulmonary exacerbations
  - Management of pulmonary complications such as hemoptysis and pneumothorax
- Smoking.
  - From diagnosis, family should be counseled to minimize environmental tobacco smoke exposure.
  - Children, especially adolescents, should be educated about the detrimental effects of tobacco smoke and illegal inhalants.
- Vaccinations.
  - Infants and children with CF should receive all routine childhood vaccinations.
  - Annual influenza vaccination is recommended for infants and children >6 months and their families.
    - Nasal spray vaccination for influenza should not be used.
- Palivizumab prophylaxis.
  - The American Academy of Pediatrics does not recommend palivizumab prophylaxis for all infants with CF.
    - It should be considered for infants with evidence of chronic lung disease or nutritional compromise.
    - The decision to pursue palivizumab prophylaxis should be based on risk/benefit and cost discussions with the family.
- Chest physiotherapy (CPT) is the cornerstone of pulmonary CF therapy.
  - Patients are prescribed a daily regimen of CPT to help them mobilize and expectorate the thick, tenacious secretions in their airways.
  - Frequency of therapy is generally increased during acute exacerbations.
  - Numerous airway clearance techniques are available.
    - Manual percussion with postural drainage
    - Autogenic drainage
    - An inflatable vest that vibrates the chest at different frequencies
    - Several handheld devices (eg, Flutter/Acapella) and therapies (eg, positive expiratory pressure)
  - Clearance techniques are designed to shear mucus off the airways and provide back pressure to stent the airways open so that secretions may be expelled.
  - Each technique has specific advantages; no single technique is superior.
- To optimize adherence, choice of therapy should be based on the method that is
  - The most effective for that patient
  - The best fit for the family's lifestyle
- Physical activity and regular exercise should be recommended as an integral part of the regimen.
  - Bronchodilators are often given before CPT to maximally dilate the airways and help facilitate clearance of secretions.
    - Patients with CF have a variable response to β-agonists.
      - Some patients exhibit a transient decline in pulmonary function, most likely secondary to collapse of bronchiectatic airways.
    - Patients with CF should be assessed for bronchodilator response by pulmonary function testing.
      - Therapy should be adjusted accordingly.
      - Long-acting β-agonists, however, may be beneficial in some patients with CF and asthma.
- Chronic inflammatory process in CF lung disease has led to considerable interest in anti-inflammatory therapies.
  - Alternate-day prednisone therapy has been shown to improve lung function in patients with chronic *P aeruginosa* infection.
    - Increased incidence of growth restriction, glucose abnormalities, and cataracts has dampened enthusiasm for this therapeutic approach.
  - Inhaled steroids and leukotriene modifiers are attractive alternatives and are widely prescribed.
    - Their use should be limited to patients with

concomitant asthma, because evidence of efficacy in CF is lacking.
- High-dose ibuprofen has been shown to decrease the rate of decline in lung function and the need for hospitalization, primarily in patients with CF who have mild lung disease.
  - The requirements for a pharmacokinetic study to determine the optimal dose of ibuprofen and concerns about safety have limited penetration of this therapy into clinical practice.
- Dornase alfa, a recombinant human deoxyribonuclease, was developed for nebulization into the airways.
  - It cleaves the viscous DNA released by dying neutrophils as part of the exaggerated inflammatory response characteristic of CF lung disease.
  - Deoxyribonuclease treatment improves the rheologic properties of the sputum.
    - It enables the patient to expectorate the sputum more easily.
    - It is generally administered once a day.
  - A multicenter study of dornase alfa showed improvement in lung function and decrease in frequency of pulmonary exacerbations with chronic use.
    - This therapy is recommended for children ≥6 years unless they have documented intolerance to dornase alfa.

- Inhaled hypertonic saline is one of the newest therapies in the CF armamentarium.
  - Inhaling a highly concentrated (7%) saline solution may increase osmotic load and stimulate water movement into the airways.
  - Improved hydration of the secretions results in better mucociliary clearance.
  - A 48-month trial of 7% saline inhaled twice daily revealed improved pulmonary function and fewer pulmonary exacerbations in treated patients compared with controls, who inhaled 0.9% saline twice daily.
    - Some patients may experience wheezing with the medication; this can be attenuated by pretreatment with a bronchodilator.
    - Recommended for children ≥6 years.
- Long-term daily antibiotic therapy is not well supported to prevent initial infection or to treat chronic bacterial infection.
  - Generally recommended for treating acute exacerbations when bacterial burden increases and patients develop associated symptoms, such as
    - Increased cough frequency and sputum production
    - Declining pulmonary function with or without radiographic changes
- Macrolide antibiotics are used to treat chronic *P aeruginosa* infection.
  - Administration of azithromycin 3 times weekly has a positive effect on lung function, weight, frequency of pulmonary exacerbations, and cough frequency in older children and adults.
    - Recommended for children ≥6 years with *P aeruginosa* persistent in airway cultures
  - A high-dose preparation of nebulized tobramycin, given twice daily in alternating months, reduces the need for hospitalization and improves pulmonary function.
    - Recommended for children ≥6 years with *P aeruginosa* persistent in airway cultures, independent of the severity or acuteness of the lung disease
  - A nebulized form of aztreonam lysine improves patient-reported respiratory symptoms, FEV_1, sputum density of *P aeruginosa,* and weight.
    - Recently approved for use in children ≥6 years with *P aeruginosa* cultured from airways
- Exacerbation of bronchopneumonia or an apparent viral respiratory illness indicates antibiotic therapy directed against the most recently cultured pathogen.
  - If patient does not have respiratory distress or hypoxemia, oral outpatient therapy may be initiated.
  - Hospitalization, intravenous (IV) antibiotics, and aggressive CPT are recommended with acute worsening of respiratory status, hypoxemia, or respiratory distress.
  - *P aeruginosa* is routinely treated with 2 antipseudomonal antibiotics.
  - Duration of antibiotic therapy depends on the severity of exacerbation.
    - Generally ≥10 days, based on the response to treatment
  - Airway clearance therapies should be increased in frequency.
  - Chronic maintenance therapies should be continued during treatment for an acute exacerbation.

- As lung disease progresses, intervals of stability between exacerbations may become shorter.
  - Patients may require supplemental oxygen therapy because of progressive hypoxemia.
  - Noninvasive ventilation may be instituted when evidence exists of carbon dioxide retention or sleep-disordered breathing.
- Lung transplantation is a final therapeutic option for the treatment of progressive, severe lung disease.
  - An inherently risky procedure with a 5-year posttransplantation survival rate of ~50%–60%.
  - Referral for lung transplantation should be made when other therapeutic options are exhausted.
  - Survival models have been developed that facilitate calculation of a patient's predicted survival without transplantation.
    - Aids selection of patients most likely to gain a survival advantage.
    - Patients should be made aware that the complicated medical regimen they follow to treat their CF-related lung disease will be replaced by a transplant medical regimen that is often equally complicated.
    - Contraindications to lung transplantation include
      - Active tuberculosis
      - HIV
      - Hepatitis B
      - Significant psychosocial dysfunction that precludes adherence to the posttransplantation medical regimen
- New drugs.
  - Ivacaftor recently received US Food and Drug Administration approval for treatment of patients with the *G551D* mutation.
    - Acts to optimize the functioning of the *CFTR* channel in patients with the *G551D* mutation by helping to increase the time that the *CFTR* channel remains open at the cell surface.
    - Clinical trials have shown that patients with the *G551D* mutation who took the drug demonstrated significant improvement in lung function, risk for pulmonary exacerbation, patient-reported respiratory symptoms, weight, and sweat chloride concentration.

Gastrointestinal Therapy

- Nutritional therapy is a cornerstone of good CF therapy.
  - Infants
    - Nutritional status, adequacy of weight gain, and caloric intake should be assessed at each visit.
    - Human milk is preferred for initial feeding; if not possible, standard infant formulas.
    - Increased calorie concentrations may be needed if weight gain is inadequate.
    - Infants and children <2 years should receive ⅛ teaspoon of table salt per day starting at diagnosis; increase to ¼ teaspoon at 6 months of age.
- Children >2 years
  - Should be evaluated at least annually by a dietitian who is knowledgeable about CF
- Frequent nutritional problems faced by adults and children with CF include
  - Lack of appetite caused by intercurrent illness
  - Inability to consume increased number of calories needed to
    - Sustain normal growth
    - Make up for lost weight
    - Achieve catch-up growth
- Fat intake should make up 35%–40% of the daily required calories, compared with <30% in people without CF.
- Infants and children with PI should receive at least 120%–130% of the recommended daily allowance of age-appropriate calories.
- Caloric requirements are higher with acute illness or exacerbation of the pulmonary disease or when catch-up growth is needed.
- Modifications are initially made to increase the caloric density of the child's regular diet.
  - High-calorie, high-fat supplements in the forms of shakes and formulas
  - Supplementation via nasogastric or gastrostomy tube if the child cannot orally consume the daily calorie requirement
- The following actions are usually adequate to prevent salt depletion syndrome:
  - Older children: increased consumption of salty foods
  - Infants: addition of salt to formula
- Patients with CF-related diabetes (CFRD) should *not* be placed on a diabetic diet.
  - A significant reduction in caloric intake might compromise overall nutritional status.

- Patients are taught how to distribute carbohydrates more equally throughout the day.
- Insulin is the therapy of choice.

- Pancreatic enzyme supplements are given with each fat-containing meal or snack.
  - Recommended dose for infants is 2,000–5,000 units of lipase per 120 mL of formula or per breastfeeding.
    - Dose may be adjusted to ≤2,500 lipase units/kg per feeding, to a maximum dose of 10,000 lipase units/kg.
    - Low-dose, enteric-coated enzyme preparations can be administered to infants.
      - Mix with a small amount of applesauce or other non-alkaline food.
  - Brand-name enteric-coated enzymes should be used exclusively.
    - Infants are at risk for developing ulceration of the oral mucosa if enzymes are not completely cleared from the oral cavity.
    - Enteric coating keeps enzymes from being destroyed by stomach acids.
    - Generic preparations should be avoided.
      - Lack of dose standardization
    - Enzyme dosing is initially based on the patient's weight.
      - Subsequently adjusted based on clinical symptoms of continued malabsorption
        - Frequency and consistency of stools
        - Perceived greasiness of stools
        - Abdominal cramping
  - Enzyme therapy for children <4 years should be initiated at a dose of 1,000 units of lipase per kilogram per meal.
  - Therapy for children ≥4 years should be started at a dose of 500 units of lipase per kilogram per meal.
  - To reduce the risk of fibrosing colonopathy, doses should generally be kept to
    - <2,500 units of lipase per kilogram per meal *or*
    - <4,000 units of lipase per gram-fat per day

Vitamin Supplements

- Children with CF should receive a standard, age-appropriate dose of non–fat-soluble multivitamins.
  - Children with PI should also receive supplements of vitamins A, D, E, and K.
  - Vitamin K is supplemented at higher levels in patients
    - With liver disease with abnormalities in clotting
    - Receiving prolonged antibiotic therapy
  - Special high-dose preparations of these vitamins are available for patients with CF.
- Dosages for vitamin supplementation.
  - 0–12 months
    - Vitamin A: 1,500 IU
    - Vitamin E: 40–50 IU
    - Vitamin D: 400 IU
    - Vitamin K: ≥0.3 mg
  - 1–3 years
    - Vitamin A: 5,000 IU
    - Vitamin E: 80–150 IU
    - Vitamin D: 400–800 IU
    - Vitamin K: ≥0.3 mg
  - 4–8 years
    - Vitamin A: 5,000–10,000 IU
    - Vitamin E: 100–200 IU
    - Vitamin D: 400–800 IU
    - Vitamin K: ≥0.3 mg
  - >8 years
    - Vitamin A: 10,000 IU
    - Vitamin E: 200–400 IU
    - Vitamin D: 400–800 IU
    - Vitamin K: ≥0.3 mg
- Acid blockers should be used as needed to treat gastroesophageal reflux.
  - Common in patients with CF.
  - Acid suppression may be beneficial for optimization of pancreatic enzyme function.
- Findings during examination should raise concern about the possible development of cirrhosis.
  - Elevated liver enzyme levels and abnormal liver function tests.
  - Detection of hepatomegaly or splenomegaly (or both).
  - Order abdominal ultrasonography.
  - Ursodeoxycholic acid has been shown to benefit patients with cholestatic diseases.
    - For example, primary biliary cirrhosis
    - Often administered in patients with CF who have hepatobiliary disease in an effort to improve bile flow and limit liver damage
- Liver transplantation is a therapeutic option when end-stage liver disease develops.

WHEN TO ADMIT

- Pulmonary exacerbations
  - Characterized by
    - Increased cough
    - Sputum production
    - Decline in pulmonary function

- Associated symptoms may include
  - Fever
  - Wheezing
  - Dyspnea
  - Malaise
  - Weight loss
- Acute changes in the chest radiograph may or may not be seen.
- The patient should be admitted for IV antibiotic therapy if response to oral antibiotic therapy is inadequate.
- If the patient is hypoxemic, he or she should be admitted to the hospital for further management.

■ Major hemoptysis
- Hemoptysis over 3–7 days of
  - >240 mL in 24 hours
  - >100 mL per day

■ Pneumothorax
- Respiratory distress *or*
- Large pneumothorax (>3 cm between apex and cupola)
- Patients with a small pneumothorax who are otherwise clinically stable may be closely observed on an outpatient basis dependent on
  - Reliability of patient and family
  - Ease of access to health care

■ Hospitalized patients should have frequent blood glucose measurements.
- Altered glucose metabolism may be present only during times of acute illness or stress, particularly in patients receiving supplemental feedings via gastrostomy tube.

WHEN TO REFER

■ All children with CF should be referred to a local CF care center for ongoing care.

■ Consultation with the regional CF care center and physicians who are experienced with the nuances of CF care is strongly recommended.

FOLLOW-UP

■ Cystic Fibrosis Foundation guidelines for newborns and infants with CF, whether diagnosed by newborn screening or later clinical presentation
- Infants should be seen monthly for at least the first year of life
  - Every 2–3 months for the second year
  - After age 2 years, quarterly or more often evaluation at an accredited CF care center

■ Monitoring
- Starting at 1–3 months of age and repeated annually, complete blood cell count with
  - Differential
  - Fat-soluble vitamins
    - Retinol
    - α-Tocopherol
    - 25-hydroxy vitamin D
  - Albumin and prealbumin (transthyretin)
  - Prothrombin time
  - Liver enzymes
- Pancreatic functional status
  - Within the first month of life in all neonates diagnosed with newborn screening
  - Fecal elastase measurement

■ Patients who do not have CFRD should have annual screening with a 2-hour glucose tolerance test beginning at age 10 years.

■ Patients with CFRD should have hemoglobin A_{1c} levels measured quarterly to assess adequacy of glucose control.

■ Patients should have at least annual measurement of renal function, particularly those who
- Are receiving long-term inhaled aminoglycoside therapy
- Receive frequent courses of IV aminoglycosides

■ All patients should receive a complete physical examination annually.
- Including hearing and vision screening
- Particularly relevant for patients receiving multiple courses of aminoglycosides because of potential ototoxicity

COMPLICATIONS

Respiratory

■ Hemoptysis and pneumothorax are both common complications of CF lung disease.
- Patients with CF may have blood-streaked sputum.
  - If the volume of blood expectorated is large (>240 mL), initiate treatment.
    - Bed rest
    - IV antibiotics
    - Cessation of any medications with anticoagulant properties
  - Bronchial artery embolization may be required if the bleeding does not resolve or becomes life threatening.
  - Resection of the bleeding segment is the therapeutic option of last resort.

- Pneumothorax occurs annually in ~1% of patients with CF.
  - Patients with respiratory distress or with a large pneumothorax (>3 cm between the apex and cupola) should be treated with a chest tube.
    - Pleurodesis is recommended for patients with recurrent large pneumothoraces.
- Children with CF are predisposed to recurrent and chronic sinusitis despite normal nasal mucociliary clearance.
  - Hypoplasia of the sinuses is a common finding.
  - Polyps may obstruct the nasal passages and contribute to the development of sinusitis.
  - The etiology of polyposis is unknown; it does not appear to be associated with allergies.
- Death most commonly results from respiratory failure and cor pulmonale caused by recurrent or chronic pulmonary infections.

Gastrointestinal

- In newborns, complications may occur because of meconium ileus.
  - Volvulus
  - Intestinal atresia
  - Meconium peritonitis
- DIOS is a common complication of CF.
  - Patients with vomiting, crampy abdominal pain, and decreased stool output should be evaluated for intestinal obstruction by imaging.
  - If DIOS is diagnosed
    - Oral intake should be withheld.
    - IV fluids or total parenteral nutrition should be initiated.
  - Obstruction may be relieved with a Gastrografin enema or oral or nasogastric administration of osmotic laxatives (polyethylene glycol).
  - Surgical intervention may be needed.
  - Other diagnostic considerations for these symptoms include
    - Appendicitis
    - Pancreatitis
    - Cholecystitis
    - Intussusception
    - *Clostridium difficile* colitis
- Liver disease leads to death in a small minority of the patient population.

Nutritional

- Patients with CF are prone to the development of CFRD, particularly in late teens and adulthood.
  - CFRD results primarily from a relative insulin deficiency caused by gradual destruction of the islet cells in the pancreas.
  - CFRD is associated with increased morbidity and mortality.
  - Patients may have the classic symptoms of diabetes.
    - Polyuria
    - Polydipsia
    - Weight loss
  - Many have minimal symptoms.
  - An element of insulin resistance has been reported.
- Patients with CFRD
  - Rarely develop diabetic ketoacidosis.
  - Are at risk for other complications of diabetes.
    - Retinopathy
    - Renal dysfunction
    - Neuropathy
- CFRD should be considered as a possible cause of
  - Poor growth
  - Delayed puberty
  - Increased frequency of pulmonary exacerbations
  - Unexplained decline in pulmonary function

Bone Density

- Osteopenia and osteoporosis are relatively common in adolescents and adults with CF, for several reasons.
  - Failure to thrive.
  - Delayed pubertal development.
  - Liver disease.
  - Physical inactivity.
  - Malabsorption of
    - Calcium
    - Magnesium
    - Vitamins D and K
  - Steroid use may further exacerbate these problems.
- Patients with decreased bone mineral density are predisposed to atraumatic fractures, especially of the spine and ribs.
- Patients may experience transient arthritis.
  - Monoarticular, pauciarticular, or polyarticular.
  - Knees, ankles, wrists, and proximal interphalangeal joints of the hands are most often affected.

Endocrine

- Pubertal development is often delayed in boys and girls with CF.
  - Delayed or blunted pubertal development results from
    - Poor nutrition and decrease in glucose tolerance, accompanied by delayed increase in sex hormone levels
- Female newborns with CF have excessive cytoplasmic and extracellular mucus.
  - Can continue into childhood.
  - Thickened cervical secretions may reduce fertility.
- Girls may have abnormal menstrual cycles.
  - Possible primary and secondary amenorrhea.
  - Increasing numbers of successful pregnancies are occurring as the population with CF ages.
- Boys with CF may have reduced testicular and epididymal size and reduced testosterone levels.
  - In most boys, bilateral absence of the vas deferens occurs secondary to obstruction and subsequent resorption of the structure.
    - Results in infertility.
    - Assisted reproductive technologies have been developed and used to treat infertility in men with CF.

PROGNOSIS

- A vicious cycle of infection and inflammation develops in the lungs of patients with CF.
  - Typically punctuated by acute exacerbation, eventually leading to bronchiectasis
  - Damages and destroys the airways
- In general, a good correlation exists between pancreatic status and genotype.
  - Patients with 2 severe mutations, such as *F508del/F508del,* are generally pancreatic insufficient.
  - Patients with 1 or 2 mild mutations are much more likely to be pancreatic sufficient; they are at increased risk of pancreatitis.
  - Individuals who are pancreatic sufficient generally have better clinical outcomes than patients with PI.

Dehydration

DEFINITION

- Dehydration is a condition in which pure water loss occurs.
- Volume depletion or hypovolemia is a condition in which extracellular fluid is lost.
- These terms are used interchangeably.

SIGNS AND SYMPTOMS

- Volume depletion
  - Measured as change in body weight from baseline.
  - Pre-illness weight is used to determine degree of weight loss due to the fluid deficit.
    - If pre-illness weight is unavailable, use
      - Pulse rate
      - Blood pressure
      - Urine output
      - Skin turgor
- Categorization of dehydration (**Table 1**)
  - Mild (3%–5% volume loss)
  - Moderate (6%–9% volume loss)
  - Severe dehydration (>9% volume loss)

DIFFERENTIAL DIAGNOSIS

- In children who only have vomiting (without diarrhea)
  - Appendicitis
  - Intussusception
  - Volvulus
  - Pyloric stenosis

DIAGNOSTIC APPROACH

- 5-point assessment
  - Volume deficit
    - History
    - Physical examination
  - Osmolar disturbance
    - Serum sodium
    - Serum osmolality
  - Acid-base disturbance
    - Blood pH
    - Partial pressure of carbon dioxide
    - Serum bicarbonate
  - Potassium
    - Serum potassium
  - Renal function
    - Blood urea nitrogen
    - Creatinine
    - Urine specific gravity

LABORATORY FINDINGS

- Laboratory tests to assess clinical condition and origin of dehydration are usually not needed in children with mild or moderate dehydration.
- For moderate to severe dehydration.
  - Serum electrolytes
    - Sodium
    - Potassium
    - Chloride
    - Bicarbonate
  - Blood urea nitrogen
  - Serum creatinine
  - Urine specific gravity
  - Serum glucose (finger prick at the bedside)
- Laboratory testing is less useful in assessing the degree of volume depletion.
- Serum bicarbonate (<17 mEq/L) differentiates moderate or severe hypovolemia from mild hypovolemia.
- Serum sodium measurements to determine type of dehydration.
  - Isonatremic (135–145 mEq/L)
  - Hyponatremic (<130 mEq/L)
  - Hypernatremic (>150 mEq/L)
- Serum potassium.
  - Falsely elevated when acidosis causes a shift from the intracellular compartment
  - Low because of losses in the gastrointestinal tract
- Urine osmolality and specific gravity.
  - May be high (often >450 mOsm/kg)
  - May be low if the patient has lost renal concentrating ability
    - Osmotic diuresis
    - Diabetes insipidus
- Bacterial cultures for children with
  - Ill appearance
  - Fever
    - ≥38.0°C (100.4°F) in infants <3 months
    - 39.0°C (102.2°F) in infants and children >3 months
  - Bloody or mucoid stools
  - Travel or exposure history suggestive of enteric pathogens
- Routine stool cultures should be discouraged.
- Studies for rotavirus antigen are needed only rarely.

TREATMENT APPROACH

- Rapid repletion of fluids.
  - Restores circulating volume
  - Reverses acidosis
  - Improves perfusion and end-organ function

Table 1. Degree of Dehydration

Parameter	Degree of Dehydration		
	Mild	Moderate	Severe
Weight loss (%), infants	5	10	15
Weight loss (%), children	3	6	>9
Skin color	Pale	Gray	Mottled
Skin turgor	May be normal	Decreased	Tenting
Mucous membranes	Slightly dry	Dry	Dry, parched, collapse of sublingual veins
Eyes	Normal	Decreased tears	Sunken, absence of tears
Central nervous system	Alert but thirsty	Irritable	Lethargic, grunting, coma
Pulse	Normal and strong	Rapid and slightly weak	Significantly tachycardic and very weak to not palpable
Capillary refill	Normal (<2 s)	2–4 s	>4 s
Blood pressure	No change	Orthostatic decrease	Shock
Urine	Normal to mildly reduced	Significantly reduced	Anuria
Volume of deficit, infants	50 mL/kg	60 mL/kg	150 mL/kg
Volume of deficit, children	30 mL/kg	100 mL/kg	>90 mL/kg

- Dehydration resulting from gastroenteritis.
  - Oral rehydration on an outpatient basis.
  - Laboratory evaluation may not be necessary.
  - Administer fluid rapidly and with the intent to restore the entire deficit in 4–6 hours.
- Proper dietary management is essential to minimize
  - Severity of symptoms
  - Duration of symptoms
- Most dehydrated children can be rehydrated successfully without resorting to parenteral (intravenous [IV] or intraosseous) therapy.
  - Parenteral therapy is reserved for severe or unusual cases.
- Combined use of an oral rehydration solution (ORS) and an appropriate regimen of refeeding is referred to as *oral rehydration therapy* (ORT).

SPECIFIC TREATMENTS

Oral Rehydration

- First choice for the conscious child who has mild or moderate dehydration.
- Fluid absorption can be promoted by enteral administration of properly designed fluids, even in the face of ongoing losses.
- ORS.
  - Fluid designed to promote water and electrolyte absorption through the cotransport system in the gut.
  - A physiologically appropriate ORS contains
    - 70–90 mEq/L sodium
    - ≤25 g/L glucose
  - An ORS typically contains
    - 20 mEq/L potassium
    - 30 mEq/L of base in the form of citrate

- The World Health Organization (WHO) formula published in 2002 specifies
  - 13.5 g/L carbohydrates
  - 75 mEq/L sodium
  - 20 mEq/L potassium
  - 30 mEq/L of bicarbonate base
  - Osmolarity of 245 mOsm/kg of water
- The WHO and the United Nations Children's Fund recommend the following properties for an ORS for global use:
  - Total osmolality 200–310 mmol/L
  - Equimolar concentrations of glucose and sodium
  - Glucose concentration ≤20 g/L (111 mmol/L)
  - Sodium concentration 60–90 mEq/L
  - Potassium concentration 15–25 mEq/L
  - Citrate concentration 8–12 mmol/L
  - Chloride concentration 50–80 mEq/L
- Juices, soft drinks, and punches usually contain much higher concentrations of sugars and almost no sodium; they are inappropriate for use as an ORS.
  - The higher sugar concentrations in these fluids may exacerbate diarrhea by presenting a large osmotic load in the intestinal lumen.
- An ORS can be used to restore fluid and electrolyte balance in children who have a wide range of initial serum sodium values.

■ Types of ORS.

- Premixed liquids.
  - Most widely available commercially in the industrialized world
  - Contain 50–70 mEq/L sodium
  - Appropriate for the mildly dehydrated child
- Significantly dehydrated infants and children need a solution with 70–90 mEq/L sodium.
- Packets of oral rehydration salts for preparation of a solution containing 90 mEq/L of sodium are available for mixing with 1 L of water to provide an inexpensive and reliable alternative.
  - These packets always should be distributed with a 1-L bottle to promote proper mixing.
- Juices, punches, and other soft drinks are inappropriate for children who have diarrhea because of the high osmotic load they introduce into the intestines.
- **Table 2** lists commonly available solutions and their compositions.

■ Rehydration phase.

- Fluids are best administered initially by a parent using a needleless syringe to introduce the solution into the child's mouth.
  - Infants: 1 tsp (5 mL) per minute
  - Toddlers: 10 mL per minute
  - Older children: 15 mL per minute

Table 2. Solutions Commonly Used in Children Who Have Diarrhea

Solution	Glucose/ Phenol (g/L)	Sodium (mEq/L)	Base (mEq/L; Citrate or Bicarbonate)	Potassium (mEq/L)	Osmolality (mmol/L)
Physiologically Appropriate Solutions					
Pedialyte	25	45	30	20	270
Ricelyte	30[a]	50	30	25	200
Rehydralyte	25	75	30	20	310
WHO and UNICEF oral replacement solution	20	90	30	20	310
Physiologically Inappropriate Solutions					
Cola	700	2	13	0.1	750
Apple juice	690	3	0	32	730
Gatorade	255	20	3	3	330

Abbreviations: UNICEF, United Nations Children's Fund; WHO, World Health Organization.

[a] Rice syrup solids.

- At a steady rate of administration, provides 300, 600, and 900 mL/h, respectively.
- Generally replaces the calculated deficit within 4–6 hours.
- The child should be reassessed frequently.
- Rehydration phase should be completed in the office, clinic, or emergency department (ED) before the child is sent home.

- Vomiting.
  - Usually not a contraindication to ORT.
  - Even when vomiting occurs, steady fluid replacement is continued orally.
  - Children usually do not discharge their entire stomach contents when they vomit.
  - As dehydration and tissue acidosis are corrected, the frequency and severity of vomiting are generally reduced.
- Maintenance.
  - After 4 hours, reassess the child's state of hydration using the original clinical criteria.
    - If dehydration is still detectable, repeat the rehydration phase based on the remaining calculated volume deficit.
    - If rehydration is complete, begin the maintenance phase.
  - Continued administration of ORS in ad lib quantities.
  - Alternate between ORS and human milk, formula, or other appropriate feedings.
  - Resume regular feedings.
  - Strong evidence suggests that the volume and duration of diarrhea are reduced when children are fed immediately following rehydration.

Parenteral and Enteral Rehydration

- Parenteral administration of initial rehydration fluids.
  - For patients who have severe dehydration (shock) fluids are administered
    - Intravenously
    - Intraosseously when line placement proves difficult
  - Rapid boluses of 0.9% sodium chloride in initial volumes of 20 mL/kg for ≤20 minutes.
  - Severely dehydrated patients may require 60–100 mL/kg before the restoration of circulating volume is apparent.
- Enteral fluid therapy may begin immediately if
  - The patient is conscious.
  - Airway protective reflexes are intact.
- Fluids are given by mouth or nasogastric tube.
- Physiologic (normal) saline solution, or 0.9% aqueous solution of sodium chloride, has 154 mEq/L of sodium, and half physiologic (normal) saline solution, or 0.45% aqueous solution of sodium chloride, has 77 mEq/L of sodium. Similarly, 0.25% aqueous solution of sodium chloride has 38 mEq/L of sodium.
  - Physicians should be aware of these sodium concentrations in IV fluids while calculating replacement of maintenance and ongoing losses of fluids and electrolytes.
  - In general, in the presence of otherwise normally functioning kidneys, most patients will do well with half physiologic saline solution or physiologic saline solution when it is used as replacement solution.
- There may be an increased incidence of iatrogenic hyponatremia with the use of hypotonic solutions in the maintenance phase of IV hydration. This has led some experts to recommended using physiologic saline solution as maintenance fluid following the initial bolus therapy.

ED

- Children who seek treatment at EDs may represent a distinct group of patients.
  - Often have seen a primary care physician earlier in the illness.
  - Physician may have attempted oral rehydration.
- Use of ORT in the ED is strongly encouraged.
  - Should always be attempted in the mild and moderately dehydrated child
- ORT in children who are sick enough to come to the ED is likely to be unsuccessful.
  - IV treatment probably will be required, especially in the older (school-aged) child in whom vomiting is the most prominent feature.
  - Such children are often too exhausted to continue with efforts to drink.
  - Reasonable to approach with a brief trial of ORT followed, if necessary, by a brief course of IV fluids and subsequent reintroduction of liquids and solids.

Children With Acute Renal Failure

- Physicians need to obtain additional testing, such as serum blood urea nitrogen, serum creatinine, urinary electrolytes, and urinary creatinine, to assess the status of kidney function and determine whether renal failure is largely caused by severe hypovolemia (prerenal azotemia) or secondary to renal damage.

- Fractional excretion of sodium (FENa) is one way of differentiating prerenal disease (a reduction in glomerular filtration rate caused solely by decreased renal perfusion) from acute tubular necrosis (ATN), the 2 most common causes of acute kidney injury.
- FENa is calculated by dividing the product of urinary sodium and serum creatinine by the product of serum sodium and urinary creatinine, expressed as a fraction.
  - In general, a FENa value <1% indicates prerenal disease, while a value >2% usually indicates ATN.
- FENa is generally more accurate than the urine sodium concentration in differentiating prerenal disease from ATN because it directly measures sodium handling.
- Children should be categorized as hypovolemic, euvolemic, or hypervolemic, and fluid replacement should be adjusted based on this categorization in conjunction with ongoing assessment of serum electrolytes, measures of renal function (blood urea nitrogen and serum creatinine), and acid-base status.
- Vigorous fluid management is recommended in hypovolemic patients to prevent those in prerenal azotemia from progressing to ATN.
  - Should include physiologic saline solution bolus along with replacement of ongoing losses and provision of maintenance fluids
- In euvolemic children, ongoing fluid losses (insensible fluid [300–500 mL/m^2 per day], urine, and gastrointestinal losses) need to be balanced with administered fluids.
  - Patients who are hypervolemic (ie, have signs of fluid overload) will require fluid removal with a trial dose of furosemide to convert the oliguric renal failure to nonoliguric state, or fluid restriction.
- It is important to restrict or even avoid potassium- and phosphorous-containing fluids in anuric or oliguric patients.
- Sodium should be replaced at 2–3 mEq/kg/d to ameliorate fluid accumulation and hypertension.

WHEN TO ADMIT

- Persistently abnormal mental status
- Persistently abnormal electrolyte levels
- Chronic diarrhea (>14 days)
- Other medical problems (eg, short gut syndrome, inflammatory bowel disease)
- Hydration status that cannot be restored or maintained after 6 hours of outpatient treatment

COMPLICATIONS

- Inadequately treated dehydration can lead to
  - Full-blown shock
  - Multi-organ dysfunction syndrome
  - End-organ damage to the kidneys, liver, and brain
  - Death
- Mild overhydration results from aggressive oral hydration.
  - Some transient periorbital puffiness.
  - 2%–3% weight gain.
  - These complications are self-limited and of no clinical consequence.
- Hypokalemia results from the loss of total body potassium as a consequence of the increased aldosterone activity in the kidney.
  - Common in severe dehydration.
  - As sodium is avidly retained, potassium is lost in the urine.
  - Hypokalemia can result in ileus.
    - May impair fluid and electrolyte absorption from the intestines
  - ORS containing 20 mEq/L potassium chloride can restore potassium balance.
- Elevated aldosterone levels caused by hypovolemia may cause
  - Renal potassium loss
  - Circulatory collapse
  - Shock
  - Irreversible organ damage
  - Death

PROGNOSIS

- Prognosis is excellent for appropriately treated diarrheal dehydration.
- Typical episodes of gastroenteritis last 3–7 days.

PREVENTION

- Extreme consequences may be prevented by early and aggressive fluid therapy.
- Risking overhydration is better than being exceptionally cautious with fluid administration.

DEFINITION

Congenital Oral Findings

- Neonatal
  - Inclusion cysts: small, white or translucent papules or cysts that develop in utero
    - Epstein pearls
      - Found along the midline raphe of the hard palate and represent epithelial remnants of palatal fusion
    - Bohn nodules
      - Heterotopic salivary gland remnants located on the buccal or lingual mucosal surface of the alveolar ridge (not the crest) or the hard palate, away from the raphe
    - Dental lamina cysts
      - Heterotopic salivary gland remnants located on the crest of the alveolar ridge
- Ankyloglossia or tongue-tie
  - Physical defect that results in limited tongue movement

Conditions Related to Tooth Emergence

- Natal: tooth eruption before birth
- Neonatal: tooth eruption within first month of life
- Eruption cyst/hematoma
  - Dome-shaped soft-tissue lesion overlying the erupting tooth that presents 1–3 weeks prior to tooth eruption
- Teething
- Atypical emergence or exfoliation
  - Tooth eruption or emergence tends to occur in a predictable pattern, although the timing can vary considerably.

Common Oral Conditions in Childhood

- Dental caries
  - One of the most common chronic childhood diseases
- Oral ulcers
  - Traumatic
  - Infectious
  - Aphthous
- Mucocele/ranula
  - Mucocele: translucent or blue pseudocyst resulting from accumulation of mucus behind a traumatized minor salivary gland
  - Ranula: mucocele that results from blockage of a larger salivary duct located on the floor of the mouth, resulting in unilateral mucus collection under the tongue
- Angular cheilitis (angular stomatitis and perlèche)
  - Inflammation at the corners of the mouth manifesting as erythema, fissures, erosion, and discomfort
- Benign migratory glossitis ("geographic tongue")
  - Loss of the filiform papillae on discrete areas, making tongue look smooth, red, and shiny
- Gingival hyperplasia
  - Hereditary or idiopathic
    - Rare, progressive enlargement of all the gingiva, beginning in early childhood
  - Inflammatory
    - Gingival overgrowth in a general or localized pattern
  - Drug induced
- Enamel defects
  - Enamel is a protective layer on the visible part of the crown of the tooth.
  - It is the hardest and most highly mineralized substance of the body.
  - Enamel formation is very sensitive, and disturbances during tooth development can result in enamel defects of primary or permanent teeth.
- Dental acid erosion
  - According to the World Health Organization: "…progressive irreversible loss of dental hard tissue that is chemically etched away from the tooth surface by extrinsic and/or intrinsic acids by a process that does not involve bacteria, which differentiates it from dental caries process."

HISTORY

Conditions Related to Tooth Emergence

- Natal or neonatal
  - Most commonly an isolated finding but can be associated with genetic syndromes such as chondroectodermal dysplasia
- Teething
  - Statistically associated findings: increased drooling, biting, chewing, sucking, rubbing of gums and ears, facial rash, crying, decreased appetite, mild temperature elevation, poor sleep.
  - No single symptom occurred in >35% of infants, and no symptom occurred >20% more often in teething than non-teething infants.
- Atypical emergence or exfoliation
  - Localized premature tooth loss is most often caused by tooth trauma and root necrosis or severe dental caries.

- Premature tooth loss affecting many or all teeth can be associated with Langerhans cell histiocytosis, endocrine disorders (hypophosphatasia or diabetes mellitus), immune disorders (disorders of neutrophil function, cyclic neutropenia), and connective tissue disorders (eg, Ehlers-Danlos syndrome).
- Emergence of permanent teeth is the stimulus for exfoliation.
  - Endocrine disorders (eg, hypothyroidism, hypopituitarism, rickets) and genetic syndromes (eg, ectodermal dysplasia, trisomy 21, cleidocranial dysostosis) will be characterized by delays in tooth loss.

Common Oral Conditions in Childhood

- Oral ulcers
  - Traumatic
    - Eating or drinking very hot foods may burn the mucosa.
    - Objects in the mouth, lip or tongue biting, abuse, self-injurious behavior.
  - Aphthous
    - More common in individuals with inflammatory bowel disease, celiac disease, immunosuppression, cyclic neutropenia, rheumatologic disorders (eg, juvenile rheumatoid arthritis, systemic lupus erythematosus), or nutritional deficiencies (eg, vitamin B_{12}, folate, iron, zinc)
- Gingival hyperplasia
  - Infiltrating: most often seen in acute monocytic leukemia
  - Drug induced: Common offenders include phenytoin, calcium channel blockers (eg, nifedipine), and cyclosporine.
- Enamel defects
  - Common risk factors
    - Adverse maternal health events during pregnancy (illnesses, nutritional deficiencies, medications)
    - Birth difficulties (preterm birth, hypoxia)
    - Early childhood illnesses (high fever, pneumonia, middle ear infection, viral infections)
    - Poor childhood nutrition (diet deficient in calcium, phosphate, or vitamins A, C, or D)
    - Trauma to the mouth or primary teeth <4 years
- Dental acid erosion
  - Extrinsic: acidic drinks, foods, and candies.
  - Intrinsic: Gastric acid is the most common (gastroesophageal reflux disease [GERD] or bulimia).
  - Anterior teeth (incisors) are predominantly affected by frequent consumption of acidic drinks, swishing or mouth holding of acidic drinks, or exposure to emesis associated with bulimia.
  - The posterior teeth (molars) are affected mainly by mastication of acidic foods, gastric acid exposure from GERD, and severe cases of bulimia.

PHYSICAL EXAMINATION

Common Oral Conditions in Childhood

- Oral ulcers
  - Aphthous
    - Round or oval, yellowish-gray ulcers with surrounding erythematous "halo"
    - Located on any mucous membrane, most commonly noted on the buccal mucosa
    - Minor
      - 80% of cases are characterized by small (2–5 mm) lesions that last 5–12 days and heal without scarring.
    - Major
      - ≤1 cm in diameter, can take several weeks to heal, and may scar
    - Herpetiform ulcers
      - <10% of cases
      - Very painful
      - Multiple 1- to 2-mm papules, vesicles, or ulcers grouped together that can coalesce to form a larger lesion
- Mucocele/ranula
  - Mucocele
    - Usually painless, located on the lower lip or buccal mucosa, ranging from very small to several centimeters in size
- Angular cheilitis
  - Manifests as erythema, fissures, erosion, and discomfort
- Benign migratory glossitis
  - Tongue is smooth, red, and shiny.
  - Areas of depression are most common on the dorsum and lateral aspects of the tongue; location and pattern vary over time, so it seems to "migrate."

- There is no effect on ability to taste, but some children report irritation with spicy or acidic foods.

DIAGNOSTIC PROCEDURES

- Mucoceles account for 11.6%–24.5% of all pediatric oral biopsies.

SPECIFIC TREATMENT

Congenital Oral Findings

- Neonatal
  - Inclusion cysts: asymptomatic, no need for further evaluation or management other than reassurance
- Ankyloglossia
  - Intervention varies from observation to surgical release.
  - Frenectomy or frenotomy, can be completed with blunt scissors, cautery, or laser.

Conditions Related to Tooth Emergence

- Natal or neonatal teeth
  - Extraction may be considered if teeth are mobile and present risk for aspiration, interfere with breastfeeding, or lead to Riga-Fede disease.
  - Observation if extraction is not needed.
- Eruption cyst/hematoma
  - No treatment is recommended; cyst will resolve spontaneously when the tooth erupts completely.
  - Provide reassurance.
- Teething
  - Recommend cold items as an anesthetic for the gums (eg, pacifiers, spoons, wet washcloths, teething rings).
  - Topical teething gels sold over the counter (OTC).
    - Often used but carry serious risks, such as local reactions, seizures with overdose, and methemoglobinemia
    - Should not be used in children <2 years
  - If necessary, parents should be instructed on proper dosing of OTC analgesic medications, such as acetaminophen or ibuprofen.

Common Oral Conditions in Childhood

- Oral ulcers
  - Traumatic: typically heal within days
  - Aphthous
    - Treatment is supportive, with bland diet.
    - Topical anesthetic creams, topical steroid creams, or mouth rinses can be tried, but benefits are not well established.
    - Recurrence is likely.
- Mucocele/ranula
  - Mucocele
    - Generally require no treatment; many resolve spontaneously.
    - If the lesion is large or uncomfortable, excision may be warranted.
  - Ranulas
    - Require marsupialization surgical excision because they are likely to become large and may interfere with swallowing, mastication, speech, or breathing.
    - Commonly recur.
- Angular cheilitis
  - Treatment often includes topical yeast treatment (nystatin) and topical antibiotic agents (mupirocin), with or without low-dose topical steroids.
  - Encourage use of thick emollient application, good oral hygiene, and trigger avoidance.
- Benign migratory glossitis
  - The condition is self-limiting, with waxing and waning.
  - No treatment is necessary.
  - Reassurance should be provided.
- Gingival hyperplasia
  - Treatment includes meticulous oral hygiene to minimize inflammation and discontinuation of any offending medication.
  - Gingivectomy should be considered if hyperplasia is severe, especially with hereditary gingival hyperplasia.
- Enamel defects
  - Aim of treatment is to reduce tooth sensitivity, strengthen teeth, and improve appearance.
  - Treatment will depend on severity of the enamel defect.
  - May include fluoride varnish for sensitivity and strengthening, dental restoration with a tooth-colored resin or crown, or extraction for severely affected teeth.
- Dental acid erosion
  - Treatment involves identifying and removing or reducing the acid source.
  - If enamel loss is causing sensitivity, dental restorative care is indicated.

WHEN TO REFER

Congenital Oral Findings

- Ankyloglossia
  - If feeding, speech development, or oral health are compromised, referral to a dentist, plastic surgeon, or otolaryngologist is indicated to evaluate the need for surgical release.

Conditions Related to Tooth Emergence

- Atypical emergence or exfoliation
  - Failure to erupt teeth by 18 months of age warrants referral to a dentist for evaluation and radiographs.

Common Oral Conditions in Childhood

- Enamel defects should be evaluated by a dentist.

COMPLICATIONS

Congenital Oral Findings

- Ankyloglossia
  - Restricted tongue movement can lead to a variety of problems.
    - Inability to latch with breastfeeding
    - Improper speech development
    - Compromised oral health
  - Constricted lingual frenum has been correlated with increased incidence of dental caries resulting from inability to remove food from the teeth.

Common Oral Conditions in Childhood

- Gingival hyperplasia
  - Can interfere with oral hygiene, tooth eruption, or chewing and can cause gingivitis.

DEFINITION

- Affects many children, including a large number whose symptoms do not rise to the level of a disorder.
- Among mental health problems associated with suicidal ideation, suicide attempts, and completed suicide.
- Depression may remit on its own or after treatment but recur spontaneously with
  - Developmental transitions
  - New stressors (positive and negative)
- Associated problems include negative effects on school performance, early pregnancy, and impairment of function in the work, social, and family environments.

HISTORY

- Children who seem depressed may have relatives who have experienced depression or other mental disorders.
  - May support thorough evaluation, especially if there is a family history of suicide
  - Can increase empathy for child's problems and provide role models for successful treatment
- Depression may come on without an apparent trigger, even among the successful and privileged.
- Often develops after one or more stresses or losses or in conjunction with prolonged anxiety.
- Most children and adolescents will experience an event that induces sadness.
  - Breakup with a friend
  - Death of a loved one or pet
  - Other losses resulting from life changes (eg, move, family member's military deployment, parents' separation)
- Symptoms may be elicited from parents or youth but, ideally, from both.
- Children and youth may not be aware of how appearance or behavior has changed in ways apparent to others.
- Symptoms and clinical findings suggesting depression include
  - Indications from history from youth or parent
    - Low or sad mood is present most days.
    - Loss of interest in school or other activities is present most days.
    - Loss of pleasure in activities formerly enjoyed (When is last time you had fun?).
    - Suicidal thoughts or acts.
    - Irritability (especially in adolescents).
    - Academic difficulties.
    - Withdrawal from friends and family.
    - Physical symptoms include
      - Headaches
      - Abdominal pain
      - Trouble sleeping
      - Fatigue
      - Poor control of a chronic illness
    - Hopelessness.
    - Poor concentration.
    - Poor or excessive sleep for developmental stage.
    - Weight loss (or failure to gain weight normally) or excessive weight gain.
    - Low self-esteem.
    - Loss of energy.
    - Agitation or slowing of movement or speech.
- Risk factors for increased susceptibility include
  - Adverse childhood experiences (eg, postpartum depression)
  - Prior trauma or bereavement
  - Family breakdown
  - Shy personality
  - Peer relationship problems
  - Breakup of a relationship; setback or disappointment
- Assessment.
  - Differentiate the symptoms from typical behavior.
  - All children may be sad or irritable at times, but, for some children, these symptoms
    - Limit their adaptability to normal peer and family situations.
    - Interfere with learning.
    - Precipitate suicidal thoughts.
- Of particular concern is major depressive disorder (MDD); *Diagnostic and Statistical Manual of Mental Disorders,* 5th Edition, criteria for MDD are summarized in Box 1.

PHYSICAL EXAMINATION

- Because many children do not spontaneously disclose symptoms, standardized psychosocial screening instruments (**Table 1**) may be used to identify children with symptoms of depression.
- Several instruments have versions to collect information from youth, parents, and teachers.
- Additional instruments can also be used to screen adolescents for depression or to help confirm findings of a general psychosocial screening.
  - Patient Health Questionnaire for Adolescents (PHQ-A)
  - PHQ-A Depression Screen

Box 1. *DSM-5* Criteria for Major Depressive Episode

A. 5 (or more) of the following symptoms have been present during the same 2-week period and represent a change from previous functioning; at least one of the symptoms is depressed mood or loss of interest or pleasure. **Note:** Do not include symptoms that are clearly attributable to another medical condition.

1. Depressed mood most of the day, nearly every day, as indicated by subjective report or observation made by others. **Note:** In children and adolescents, can be irritable mood.
2. Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by subjective account or observation).
3. Significant weight loss when not dieting or weight gain (eg, a change of >5% of body weight in a month), or decrease or increase in appetite nearly every day. **Note:** In children, consider failure to make expected weight gain.
4. Insomnia or hypersomnia nearly every day.
5. Psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down).
6. Fatigue or loss of energy nearly every day.
7. Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick).
8. Diminished ability to think or concentrate, or indecisiveness, nearly every day (by subjective account or as observed by others).
9. Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide.

B. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

C. The episode is not attributable to the physiologic effects of a substance or to another medical condition. **Note:** Criteria A–C represent a major depressive episode.
Note: Responses to a significant loss (eg, bereavement, financial ruin, losses from a natural disaster, a serious medical illness or disability) may include the feelings of intense sadness, rumination about the loss, insomnia, poor appetite, and weight loss as noted in Criterion A, which may resemble a depressive episode. Although such symptoms may be understandable or considered appropriate to the loss, the presence of a major depressive episode in addition to the normal response to a significant loss should also be carefully considered. This decision inevitably requires the exercise of clinical judgment based on the individual's history and the cultural norms for the expression of distress in the context of loss.

D. The occurrence of the major depressive episode is not better explained by schizoaffective disorder, schizophrenia, schizophreniform disorder, delusional disorder, or other specified and unspecified schizophrenia spectrum and other psychotic disorders.

E. There has never been a manic episode or a hypomanic episode. **Note:** This exclusion does not apply if all of the manic-like or hypomanic-like episodes are substance induced or are attributable to the psychological effects of another medical condition.

From American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 5th ed. Arlington, VA: American Psychiatric Association Publishing; 2013, with permission.

- Beck Depression Inventory—Primary Care (also known as Fast Screen)
- Modified Patient Health Questionnaire-9 (PHQ-9)

- Differentiate the use of these tools for screening at routine visits from use for refining existing concerns.
- For screening, they have relatively low sensitivity and positive predictive value.
  - Positive results need further discussion.
  - Negative results may not be reassuring.
- When used to follow up on existing concerns, results must still be discussed with families but are more likely to indicate the nature and severity of the child's problems.

Table 1. General Psychosocial Screening Results Suggesting Depression

Screening Instrument	Score Suggesting Depression
Pediatric Symptom Checklist (PSC)	• Total score ≥24 for children ≤5 y • ≥28 for those 6–16 y • ≥30 for those ≥17 y AND • Further discussion of items related to depressive symptoms confirms a concern in that area.
PSC-17	• Internalizing subscale is ≥5. AND • Further discussion of items related to depressive symptoms confirms a concern in that area.
Strengths and Difficulties Questionnaire (SDQ)	• Total symptom score of >19 • Emotional symptom score of 7–10 (See instructions at www.sdqinfo.com.) • Impact scale score of 1 (medium impairment) or ≥2 (high impairment) AND • Further discussion of items related to depression confirms a concern in that area.

- Functional assessment tool will help determine whether the child's functioning is significantly impaired.
  - Strengths and Difficulties Questionnaire (SDQ)
  - Columbia Impairment Scale (CIS)
- Tool to assess the effect of the child's problem on other members of the family.
  - Caregiver Strain Questionnaire (CGSQ)

DIFFERENTIAL DIAGNOSIS

- Sleep deprivation
  - Sleep problems can cause irritability and labile mood.
  - Depression may contribute to difficulty sleeping.
- Somatic complaints
  - Depressed children may present with a variety of somatic complaints (eg, gastrointestinal symptoms, headaches, chest pain).
  - Acute or chronic medical conditions or pain syndromes may cause depression.
- Learning problems or disabilities
  - If symptoms of depression are associated with problems of school performance, the child may be experiencing learning difficulties.
- Exposure to adverse childhood experiences.
  - Trauma.
  - Violence.
  - Natural disaster.
  - Separation from a parent.
  - Parental divorce or separation.
  - Parental substance use.
  - Neglect.
  - Physical, emotional, or sexual abuse.
  - These children are at high risk of developing emotional difficulties.
    - Adjustment disorder
    - Posttraumatic stress disorder (PTSD)
    - Depression
  - Denial of trauma symptoms does not mean trauma did not occur.
  - Questions about these events should be repeated as a trusting relationship is established.
- Maltreatment
  - Children who have experienced neglect or physical, emotional, or sexual abuse are at high risk of developing emotional difficulties, such as depression
- Anxiety
  - Depression often co-occurs with anxiety.

- Bereavement
  - Most children will experience the death of a family member or friend sometime in their childhood.
  - Other losses may also trigger grief responses (sadness, despair, insecurity).
    - Separation or divorce of parents
    - Relocation
    - Change of school
    - Deployment of a parent in military service
    - Breakup with a girlfriend or boyfriend
    - Remarriage of parent
  - Losses may make the child more susceptible to impaired functioning at the time of subsequent losses.
- Physical illness and medication side effects
  - Medical issues that can mimic or provoke symptoms of depression include
    - Hypothyroidism
    - Lupus
    - Chronic fatigue syndrome
    - Diabetes
    - Anemia
  - Children with any chronic medical condition are more likely to experience depression than peers.
    - Depression may contribute to poor management of the condition.
  - Medications commonly used in adolescence can be associated with depression.
    - Acne preparations
    - Oral contraceptives
    - Interferon
    - Corticosteroids
- Substance use
  - Children with symptoms of depression may self-medicate with alcohol, nicotine, or other drugs.
  - Children using substances may manifest depression and deteriorating school performance.
- Conduct or oppositional disorders
  - Oppositional children may manifest depressive symptoms.
  - Children with conduct problems are at higher risk for suicide.
- Psychosis
  - Depression can be complicated by problems with thinking that go beyond the distortions or hopelessness of low mood.
    - Delusions (strongly held and usually odd false beliefs about others, one's body, or one's self)
    - Paranoia (strongly felt and unjustified concerns that others are following or intend harm)
    - Hallucinations (seeing or hearing things that others don't hear or see)
  - Individuals often don't volunteer that they are having these thoughts.
  - Asking is important if the person's interactions seem unusual (Do you ever feel your eyes or ears play tricks on you?).
- Bipolar disorder
  - Adults and older adolescents with bipolar disorder may have markedly varying low mood (depression) or high mood (mania), cycling over weeks or months.
  - Diagnosis of bipolar disorder in children remains controversial.
  - Consider bipolar disorder in
    - Children who cycle through low and high moods very rapidly
    - Children with
      - Explosive or destructive tantrums
      - Dangerous or hypersexual behavior, aggression
      - Irritability
      - Bossiness with adults
      - Driven creativity (sometimes depicting graphic violence)
      - Excessive talking
      - Separation anxiety
      - Chronic depression
      - Sleep disturbance
      - Delusions
      - Hallucinations
      - Psychosis
      - Talk of homicide or suicide

TREATMENT APPROACH

- Suicidal intent is an emergency requiring immediate treatment and close supervision at all times.
- Care can begin in the primary care setting from the time symptoms are recognized, even if
  - They do not rise to the level of a disorder.
  - Referral to a mental health specialist is ultimately part of the care plan.
- For youth with a diagnosis of moderate to severe MDD, data indicate
  - Superior efficacy of cognitive behavior therapy (CBT) plus a selective serotonin reuptake inhibitor (SSRI) compared with CBT alone or an SSRI alone

SPECIFIC TREATMENT

- A variety of evidence-based interventions are available to treat depressive disorders in children and adolescents (**Table 2**).
- Engage youth and family in care.
  - The process may require multiple primary care visits.
  - Reinforce strengths of the youth and family and identify barriers (eg, stigma, family conflict, resistance to treatment).
    - Good relationships with at least one parent or important adult
    - Prosocial peers
    - Concerned or caring family
    - Help seeking
    - Connection to positive organizations
  - Use "common factors" techniques to build a therapeutic alliance with the child and family (**Box 2**).
  - Regardless of other roles, the primary care physician can encourage a positive view of treatment.
- Provide psychoeducation.
  - Depression is common and not the result of lack of coping ability or personal strength.
  - Talk about family history of depression.
    - May reduce stigma and increase empathy and a willingness to seek care
    - May also be met with resistance
  - To help family members understand the disorder, highlight that
    - The youth is not making the symptoms up.

D

Table 2. Psychosocial and Psychopharmacologic Treatments for Depression

Psychosocial Treatments for Depression (as of April 2017)		
Cluster Area	**Level 1—Best Support**	**Level 2—Good Support**
Depressive or withdrawn behaviors	• Cognitive behavior therapy (CBT) • CBT and medication • CBT with parents • Client-centered therapy • Family therapy	• Cognitive behavioral psychoeducation • Expression • Interpersonal therapy • Motivational interviewing/engagement and CBT • Problem-solving • Relaxation
Suicidality	None	• Attachment therapy • Counselors care • Counselors care and support training • Interpersonal therapy • Multisystemic therapy • Parent coping/stress management • Psychodynamic therapy • Social support
US Food and Drug Administration–Approved Psychopharmacologic Interventions		
Diagnostic Area	**Psychopharmacologic Intervention**	
Major depressive disorder (MDD)	• Selective serotonin reuptake inhibitor (SSRI) (fluoxetine and escitalopram are currently the only drugs approved by the FDA for treating MDD among youth). • Data indicate superior efficacy of combination CBT and SSRI versus CBT or SSRI alone.	

PracticeWise. Evidence-Based Child and Adolescent Psychosocial Interventions. https://www.aap.org/en-us/Documents/CRPsychosocialInterventions.pdf. Accessed April 4, 2017.

For US Food and Drug Administration–approved interventions, go to www.fda.gov/ScienceResearch/SpecialTopics/PediatricTherapeuticsResearch/default.htm.

Box 2. HELP Build a Therapeutic Alliance

H = Hope

Increase the family's hopefulness by describing your realistic expectations for improvement and reinforcing the strengths and assets you see in the child and family.

E = Empathy

Communicate empathy by listening attentively.

L^2 = Language, Loyalty

Use the child's or family's own language to reflect your understanding of the problem as they see it and to give the child and family an opportunity to correct any misperceptions.

Communicate loyalty to the family by expressing your support and your commitment to help.

P^3 = Permission, Partnership, Plan

Ask the family's permission for you to ask more in-depth questions or make suggestions for further evaluation or management.

Partner with the child and family to identify any barriers or resistance to addressing the problem, find strategies to bypass or overcome barriers, and find agreement on achievable steps aligned with the family's motivation.

Establish a plan (or incremental first step) through which the child and family will take some action(s), work toward greater readiness to take action, or monitor the problem, then follow up with you, based on the child's and family's preferences and sense of urgency. (The plan might include, for example, gathering information from other sources such as the child's school, making lifestyle changes, applying parenting strategies or self-management techniques, reviewing educational resources about the problem or condition, initiating specific treatment, seeking referral for further assessment or treatment, or returning for further family discussion.)

From American Academy of Pediatrics. *Addressing Mental Health Concerns in Primary Care: A Clinician's Toolkit* [CD-ROM]. Elk Grove Village, IL: American Academy of Pediatrics; 2010.

- What looks like laziness or crossness can be symptoms of depression.
- The hopelessness of depression is a symptom and not an accurate reflection of reality.
- This negative view of the world and future possibilities can be hard to penetrate.
- Treatment works (although it can take several weeks for improvement).
- The affected individual is often the last person to recognize that improvement has taken place.

- Encourage families to
  - Address risk factors for depression and suicidal acts.
  - Remove weapons from the home or secure them.
  - Make a careful survey for potentially lethal medications, household chemicals, and pesticides.
- Social networks/social media.
  - Social networks allow spread of suicidal and depressive thoughts.
  - Electronic communication promotes isolation at the same time as it seems to be increasing connectedness.
  - Help parents monitor and limit e-mail, texts, and social media posts until the child has recovered.
- Talk about the variety of treatments, including psychosocial care and medications (for teens).
- Discover if teens or parents are anxious that the discussion is leading to a suggestion they would not be willing to accept.

■ Encourage healthy habits.

- Encourage
  - Exercise
  - Outdoor play
  - Healthy diet
  - Sleep
  - Limiting screen time
  - One-on-one time with parents
  - Praise for positive behavior
  - Acknowledgment of the youth's strengths

- "Prescribe pleasure" by telling youth and families that caring for oneself is an important part of self-care.

- Reduce stress.
  - Consider the youth's social environment.
    - Family social history
    - Parental depression screening
    - Results of any family assessment tools administered
    - Reports from child care or school
  - Are there grief and loss issues in the youth or other family members?
    - Grief and loss are virtually universal childhood experiences.
    - Children vary widely in their reactions to these events, depending on
      - Developmental level
      - Temperament
      - Prior state of mental health
      - Coping mechanisms
      - Parental responses
      - Support system
    - Helpful measures to counteract grief include
      - Supportive counseling.
      - Explaining to children and adolescents what they might reasonably expect.
      - Inviting them to participate in the funeral or other ceremonies to the level they feel comfortable.
      - Active listening while the child or adolescent expresses his or her grief.
      - Providing guidance about the grief process.
      - Identifying and addressing feelings of guilt.
      - Reluctance to increase parental sadness may necessitate time alone with the clinician when a parent is also grieving.
      - Follow up and provide opportunities to assess for more serious reactions (eg, complicated bereavement, depression, PTSD).
    - Provide referral to community resources, if appropriate.
    - The effects of profound losses (eg, death or removal of a sibling or parent during childhood) last a lifetime.
    - The clinician will need to view future physical and mental health issues in the family through the prism of this loss.
    - Overlooking such experiences and failing to follow up on the child's and family's progress after a traumatic event are lost opportunities to connect with the child and family around important mental health issues.
  - Is the youth or family experiencing unusual stress?
    - Consider reasonable and short-term changes in demands and responsibilities (eg, negotiating extensions for assignments or other ways of reducing stress at school).
    - Seek help for others in the family who are distressed.
    - Help the parent who is grieving address his or her own needs and find additional support for the youth and other family members.
  - Are there weapons or medications in the house?
    - Remove guns from the home.
    - Remove, destroy, or secure
      - Other weapons
      - Medications (including over-the-counter preparations and acetaminophen)
      - Alcohol
    - In farm communities, toxic products (eg, insecticides, fertilizers) may need to be secured.
    - Dissuade depressed individuals from operating dangerous machinery or engaging in other activities that require care and normal risk aversion to avoid injury.
- Offer initial intervention(s) to address the depression symptoms.
  - Evidence-based psychosocial interventions (see **Table 2**) apply to the care of children with mild or emerging depressive symptoms and to those with impairing symptoms that do not rise to the level of a disorder.
    - Also serve as initial management of children with a depressive disorder while awaiting specialty care.
  - Help the youth to develop cognitive and coping skills.
  - Find agreement with the youth and family on a description of the problem.
    - Many negative thoughts can be empathetically challenged and looked at from another perspective.
    - Helpful metaphors include
      - "Long journeys start with a single step."
      - "The glass is half full, not half empty."
  - Relaxation techniques and visualization can be helpful for sleep and anxiety-provoking situations.
    - Ask the youth what he or she does to feel better or relax and, if appropriate, prescribe more of that (behavioral activation).
    - Encourage a focus on strengths.
    - Distraction is also good therapy.

- Help the youth to develop problem-solving skills.
  - Determine what small achievable act would help the youth feel that he or she is on the way to overcoming problems.
  - Suggest that the youth list difficulties, prioritize, and concentrate on one at a time.
  - Avoid downplaying social crises that are important to the young person.
  - Offer to help evaluate the options as the youth sees them, seeking, if there is an opening, permission to offer alternatives.
- Rehearse behavior and social skills.
  - Reactions to particular situations or people often seem to trigger or maintain low mood.
  - If these can be identified, assist in developing and practicing means of avoidance or alternative responses.
  - Practice doing things and thinking thoughts that improve mood.
  - Create a safety and emergency plan.
- In partnership with the family, develop a treatment plan that includes a listing of telephone numbers to call in the event of a sudden increase in distress.
  - Number for a suicide or depression hotline
  - On-call telephone number for the practice
  - Area mental health crisis response team contact information
- Instruct family to proactively remove lethal means and monitor for suicide risk factors.
  - Increased agitation
  - Stressors
  - Loss of rational thinking
  - Expressed wishes to die
  - Previous attempts
  - Comorbid conduct disorder or aggressive outbursts

WHEN TO REFER

- Youth with MDD would ideally receive treatment from a licensed therapist with training in CBT.
- Involve specialist(s) if the youth does not respond to initial interventions or if
  - Preadolescent child manifests depression or suicidal ideation.
  - Adolescent with depressive symptoms has
    - Made a prior suicide attempt
    - Developed a plan (especially with means available)
    - Knew a friend or acquaintance who committed suicide
  - Adolescent's functioning is significantly impaired.
  - Symptoms are threatening achievement of developmentally important goals (eg, attending school, spending time with friends).
  - Adolescent has mental health comorbidities, such as substance use or evidence of an emerging psychotic disorder.
  - Adolescent has symptoms of bipolar disorder.
  - Depressive symptoms were preceded by serious trauma.
- Youth referred for mental health specialty care complete the referral process only 61% of the time.
  - Significantly smaller numbers persist in care.
- Approaches to improving the referral process include making sure the family
  - Is ready for this step in care
  - Has some idea of what the specialty care will involve
  - Understand what the clinician's ongoing role may be
- If the youth is referred to mental health specialty care for a depressive disorder, the clinician may be responsible for
  - Initiating medication or adjusting doses
  - Monitoring response to treatment
  - Monitoring adverse effects
  - Engaging and encouraging the youth's and family's positive view of treatment
  - Coordinating care provided by parents, school, medical home, and specialists

WHEN TO ADMIT

- A preadolescent child manifests depression or suicidal ideation.
- An adolescent with depressive symptoms has made a prior suicide attempt, developed a plan (especially with means available), or knew a friend or acquaintance who committed suicide.
- An adolescent's functioning is significantly impaired.

FOLLOW-UP

- Monitor progress toward therapeutic goals.
  - Child care, preschool, or school reports
  - Screening instruments that gather information from multiple reporters (youth, parent, teacher)
- Help family understand that it is not uncommon for treatment to be successful for a period and then seem to lose effectiveness.
  - New stresses or demands
  - Letup on treatment

- Consider new treatments or diagnoses if existing treatment does not help.
- As school demands increase, learning issues may need to be considered.

COMPLICATIONS

- Determining suicide risk.
  - Family members (present or past generations) who have had depression or bipolar disorder or who have attempted suicide
  - Substance use
  - A model among peers or celebrities known to the youth
  - Recent traumatic or shameful episode
  - A past attempt
    - Single strongest risk factor for future attempts
- Interview questions.
  - "Have you ever felt bad enough that you wished you were dead?"
  - "Have you had any thoughts about wanting to kill yourself?"
  - "Have you ever tried to hurt or kill yourself or come close to hurting or killing yourself?"
  - "Do you have a plan?"
  - "Do you have a way to carry out your plan?"
- Think of inquiry as a staged process.
  - A significant minority of adolescents have transient suicidal thoughts or "passive death wishes."
    - Thoughts that perhaps death would be a way out of problems or stresses but without thinking of a way to harm themselves.
    - Absent the risk factors discussed previously, these youth likely need exploration of stressors and assessment for mental health problems.
  - A smaller group will have thought about ways of harming themselves but without a concrete plan or making any preparations.
    - Absent past attempts, ongoing stressors, or substance use, these youth need support and further evaluation but are not at high risk.
  - Youth with plans for self-harm, or who have gathered or identified the means, are at high risk.
    - They require a short-term plan for safety and an urgent mental health evaluation.

PREVENTION

- Some evidence suggests initial onset or recurrence of depression may be preventable.
- Protective measures include
  - Nurturing care during the critical first years of life
  - Warm and confiding family relationships
  - Active coping strategies for predictable stressors
  - A sense of self-efficacy through learning to work through problems
  - Regular patterns of sleep and exercise
- If parents have mental health problems (especially depression)
  - Help children understand and cope with changing parental mood and behavior.
- If a child or youth has received treatment for depression
  - Continue treatment beyond the early stages of recovery to reduce risk of relapse or recurrence.

Diabetes Mellitus

DEFINITION

- Diabetes mellitus
  - Heterogeneous group of conditions with diverse underlying pathophysiologic factors that result in elevated blood glucose levels
- Type 1 diabetes (T1D)
  - Elevated blood glucose level caused by an absolute insulin deficiency
  - Type 1A
    - Classic form caused by autoimmune destruction of the pancreatic β cells
  - Type 1B
    - Non–immune-mediated severe insulin deficiency caused by such conditions as cystic fibrosis or pancreatectomy
- Type 2 diabetes (T2D)
  - Caused by a relative insulin deficiency, peripheral resistance to the action of insulin, or both
- Maturity-onset diabetes of the young (MODY): defect in pancreatic β cells

SIGNS AND SYMPTOMS

- T1D
  - Acute or subacute onset of symptoms (days to weeks)
    - Abdominal pain
    - Nausea
    - Polyuria
    - Polydipsia
    - Significant weight loss despite an increasing appetite
- Severe ketoacidosis
  - Tachypnea
  - Fruity odor to the breath
- Severe diabetic ketoacidosis
  - Altered mental status
  - Seizures
- Physical examination
  - May be helpful in the case of suspected diabetes but will not substitute for laboratory confirmation of the diagnosis.
  - T1D and T2D have no pathognomonic physical findings.
  - Physical findings are consistent with the degree of insulin deficiency and duration of the disorder.
    - Dehydration
    - Tachycardia in some cases
- T2D
  - More insidious than T1D in onset
    - Patients may be asymptomatic.
    - Polyuria.
    - Polydipsia.
  - Signs of insulin resistance
    - Acanthosis nigricans.
    - Weight loss may be apparent, but patients are invariably obese at the time of diagnosis.
    - Hypertension.
- MODY
  - Clinical course varies considerably among the different forms.
  - Suspect if
    - T2D develops at a young age in a thin individual.
    - Family history is suggestive of autosomal-dominant inheritance.
  - The specific type of MODY should be characterized if the diagnosis is made or suspected.

DIFFERENTIAL DIAGNOSIS

- Hyperglycemia from any cause can lead to symptoms related to an osmotic diuresis.
- Glycosuria: Glucose may be seen in the urine of some normoglycemic individuals, and glycosuria alone cannot be used to diagnose diabetes mellitus.
- Because of the glycosuria, the child with T1D or T2D loses calories, which manifests as weight loss in the face of increased appetite.

DIAGNOSTIC APPROACH

- Criteria for diagnosis[1]
  - Symptoms of diabetes include
    - Polyuria
    - Polydipsia
    - Unexplained weight loss
  - Causal (ie, any time of day without regard to time since the last meal) serum glucose level ≥200 mg/dL *or*
  - Fasting (≥8 hours) serum glucose level ≥126 mg/dL *or*
  - Serum glucose level ≥200 mg/dL 2 hours after an oral glucose challenge.
    - Glucose load should contain 75 g of glucose for adults or 1.75 g/kg in children (maximal dose, 75 g [A dose of 1.75 g/kg of glucose has been suggested when performing an oral glucose tolerance test in children, but this dose is less well established than the 75-g dose used in adults.]) *or*
    - Hemoglobin (Hb) A_{1c} ≥6.5%

- T2D can be asymptomatic, and the diagnosis may be made only as a result of screening.

LABORATORY FINDINGS

- Serum glucose level
  - ≥126 mg/dL after an 8-hour fast is diagnostic.
- Oral glucose tolerance test
  - More costly and labor intensive than serum glucose level.
  - May identify some individuals with diabetes who have a fasting serum glucose level <126 mg/dL.
- Blood and urine ketone levels
  - Traditionally associated with T1D but occasionally present in patients with T2D
- Insulin and C-peptide concentrations
  - Generally low in established T1D.
  - Low C-peptide concentrations can be seen in MODY and T2D with glucose toxicity, which may make it less helpful at time of diagnosis.
- Antibody measurements (T1D)
  - Sensitivity and specificity are not sufficient to warrant routine clinical use.
  - Antibodies can be elevated in patients who may not develop disease for many years or ever.

CLASSIFICATION

Classification of Disorders of Glycemia[2]

- T1D
  - β-Cell destruction, leading to absolute insulin deficiency
  - Type 1A
  - Type 1B
- T2D
  - Relative insulin deficiency with or without insulin deficiency
- Other types of diabetes/hyperglycemia
  - Genetic defects of β-cell function
  - MODY
    - Chromosome 12, hepatocyte nuclear factor (HNF)-1a (MODY3)
    - Chromosome 7, glucokinase (MODY2)
    - Chromosome 20, HNF-4a (MODY1)
    - Chromosome 13, insulin promoter factor-1 (MODY4)
    - Chromosome 17, HNF-1b (MODY5)
    - Chromosome 2, neuro D1 (MODY6)
    - Mitochondrial DNA
    - Others
  - Genetic defects in insulin action
    - Type A insulin resistance
    - Leprechaunism
    - Rabson-Mendenhall syndrome
    - Others
  - Diseases of the exocrine pancreas
    - Pancreatitis
    - Trauma/pancreatectomy
    - Neoplasia
    - Cystic fibrosis
    - Hemochromatosis
    - Others
  - Endocrinopathies
    - Acromegaly
    - Cushing syndrome
    - Glucagonoma
    - Pheochromocytoma
    - Hyperthyroidism
    - Somatostatinoma
    - Aldosteronoma
    - Others
  - Drug or chemical induced
    - Vacor
    - Pentamidine
    - Nicotinic acid
    - Glucocorticoids
    - Thyroid hormone
    - Diazoxide
    - Thiazides
    - Others
  - Infections
    - Congenital rubella
    - Cytomegalovirus
    - Others
  - Uncommon forms of immune-mediated diabetes
    - Stiff-man syndrome
    - Anti-insulin receptor antibodies
    - Others
  - Gestational diabetes mellitus

TREATMENT APPROACH

- Therapy must be tailored to the specific underlying pathophysiologic condition.
  - Individualized patient education and support is imperative for success.

- T1D requires an integrated multidisciplinary team.
  - Physicians
  - Nurses
  - Diabetes educators
  - Dietitians
  - Social workers
  - Psychologists
  - School or child care personnel
- Insulin therapy.
  - Required in patients with T1D.
  - May not always be necessary for children with T2D.
  - Safe and effective choice if it is not initially clear whether the patient has T1D or T2D.
- Diabetes caused by excess glucocorticoids or other medications.
  - Dose reduction or elimination of the drug (if possible) may be all that is required.

SPECIFIC TREATMENTS

Patient Education

- Critical to safe and successful diabetes management
- Must be developmentally appropriate
  - Teenagers should be able to assume more responsibility for their care than young children.

T1D

- The goal is to safely achieve as near euglycemia as possible while minimizing adverse events, primarily hypoglycemia.
  - Glycemic control improves outcomes with regard to
    - Microvascular complications
    - Macrovascular complications
    - Reduction in progression of diabetic retinopathy
- American Diabetes Association age-adjusted guidelines for glycemic control.[1]
  - Age 0–6 years
    - Premeal serum glucose 100–180 mg/dL.
    - Bedtime or overnight serum glucose 110–200 mg/dL.
    - HbA_{1c} 8.5%.
    - Less tight control is recommended for younger children.
      - Risks of hypoglycemia may be greater.
      - Advantages of very tight control have not been proven.
  - Age 6–12 years
    - Premeal serum glucose 90–180 mg/dL
    - Bedtime or overnight serum glucose 100–180 mg/dL
    - HbA_{1c} 8.0%
  - Age 13–19 years
    - Premeal serum glucose 90–130 mg/dL
    - Bedtime or overnight serum glucose 90–150 mg/dL
    - HbA_{1c} 7.5%
  - Adults
    - Premeal serum glucose 90–130 mg/dL
    - HbA_{1c} 7%
- Lower HbA_{1c} values may be safely obtained in select patients in whom the risk of severe hypoglycemia is deemed low.
- Pregnancy.
  - Postprandial glucose targets are widely used in the management of diabetes during pregnancy.
    - These targets are not commonly used outside pregnancy because their value has not been studied rigorously in children.

T2D

- Treatment options available for patients with T2D are more diverse than for those with T1D.
  - Although many effective medications with a variety of mechanisms of action are available, few are indicated in children.
  - Therapy must be tailored to fit the clinical situation of the patient.
- Weight loss and exercise.
  - Can significantly improve insulin sensitivity.
  - Appropriate in the asymptomatic patient with a reference or near-reference HbA_{1c} level.
  - May be adequate for maintenance of glycemic goals in patients who will adhere to dietary and exercise guidelines.
  - Lifestyle modification intervention has been shown to reduce development of T2D in adults by 58% over 2.8 years of follow-up.
- Pharmacologic intervention.
  - Consider for patient with
    - Symptomatic hyperglycemia
    - Significantly elevated HbA_{1c} level
  - No pharmacologic intervention is a substitute for lifestyle intervention and medical nutrition therapy.
  - Insulin.
    - The only medication approved for the treatment of diabetes in children at all ages.

- Most children with T2D can improve glycemic control with less intensive programs than are needed for patients with T1D.
- Once- or twice-daily, intermediate- or long-acting insulin may be sufficient.
- When a patient is experiencing symptomatic hyperglycemia and has a significantly elevated HbA_{1c} level (>8%–9%), insulin therapy is usually required.

- Metformin.
  - The only oral agent approved for use in children.
  - In the recently completed TODAY (Treatment Options for Type 2 Diabetes in Adolescents and Youth) trial to maintain glycemic control in youths with T2D, metformin alone achieved durable glycemic control in only about half of adolescents enrolled.
  - In addition to lifestyle changes, metformin should be considered first-line pharmacologic therapy for children with T2D.
  - Advantages.
    - Safe and effective in lowering HbA_{1c} levels when used appropriately
    - Does not induce hypoglycemia when used alone
    - Weight stabilization or mild weight loss
  - Gastrointestinal disturbance is the major side effect.
    - Largely prevented by slow titration of the dose
  - Contraindications.
    - Significant liver disease or renal impairment

Specific Insulin Programs

- All patients taking insulin will need to have an individualized plan for
  - Type and dose of insulin
  - Timing of injections
  - Frequency of home glucose monitoring
- Typical doses of insulin in children include
  - 0.5–1 unit of insulin per kg per day.
  - During puberty, children require higher insulin doses to achieve the same control.
  - For patients with T1D
    - Intermediate- or long-acting insulin is used as the basal insulin.
    - A short-acting insulin bolus is used to control the post-meal glucose increase.
- Short acting
  - Regular
    - Onset: 30 minutes
    - Peak: 2–4 hours
    - Duration: 4–6 hours
  - Lispro
    - Onset: <15 minutes
    - Peak: 1 hour
    - Duration: 3–4 hours
  - Aspart
    - Onset: <15 minutes
    - Peak: 1 hour
    - Duration: 3–4 hours
  - Glulisine
    - Onset: <15 minutes
    - Peak: 1 hour
    - Duration: 3–4 hours
- Intermediate acting
  - NPH
    - Onset: 2–4 hours
    - Peak: 4–6 hours
    - Duration: 10–16 hours
  - Lente
    - Onset: 3–4 hours
    - Peak: 6–10 hours
    - Duration: 10–20 hours
- Long acting
  - Glargine
    - Onset: 2–3 hours
    - Peak: none
    - Duration: ≥24 hours
  - Detemir
    - Onset: 1–2 hours
    - Peak: 3–9 hours
      - Higher doses result in delayed peak and longer duration of action.
    - Duration: 6–23 hours
      - Higher doses result in delayed peak and longer duration of action.
- Split-mixed program
  - Commonly used in younger patients in whom fewer injections may be desirable.
  - A short-acting and an intermediate-acting insulin are mixed.
    - Given as a single injection before breakfast and again before the evening meal.
    - Higher doses are required in the morning compared with the evening.

- Typical ratio is
  - ⅔ to ¾ of the total daily dose given in the morning and the remainder in the evening.
  - ~⅔ of the morning dose is intermediate-acting insulin.
    - The rest is short-acting insulin.
  - Equal amounts of intermediate- and short-acting insulin are given with the evening meal.
- Prevention of hypoglycemia.
  - A snack at bedtime can prevent nighttime hypoglycemia.
  - Intermediate-acting insulin will have its peak action in the early morning hours.
  - Evening dose of intermediate-acting insulin can be given at bedtime to help prevent this complication.
- Limitations.
  - Achieving adequate glycemic goals is sometimes not possible.
  - Program requires patients to be on a fixed diet with respect to timing and nutrient content at each meal.

- Multiple daily injection (MDI) program
  - Intermediate- or long-acting insulin as the basal insulin.
  - Short-acting insulin as a bolus with each meal.
    - Requires 3–4 (or more) injections each day.
    - More flexibility in timing and content of meals than split-mixed programs.
  - Basal insulin.
    - Constitutes approximately half of the total daily dose
    - Usually given in the evening
  - The amount of short-acting insulin given with each meal depends on the amount of carbohydrate consumed at that meal.
    - If the patient has been prescribed an exchange diet with a fixed amount of carbohydrate for each meal, the dose of insulin will be the same from day to day.
    - Patients who vary carbohydrate consumption will need to adjust insulin accordingly.
    - This regimen employs a correction dose of short-acting insulin if the premeal glucose is outside the target range.
- Continuous subcutaneous insulin injection (CSII) program
  - Cartridge filled with short-acting insulin serves as the basal and bolus insulin.
    - Insulin is delivered through tubing connected to a flexible plastic cannula, which is inserted subcutaneously.
  - Advantages.
    - Pump can be concealed under a person's clothing.
    - Multiple basal rates can be programmed for patients whose basal insulin requirements are not constant throughout the day.
    - This feature is not available with a split-mixed or MDI program.
    - Tubing and cannula are changed every 2–3 days, significantly reducing the number of injections required.
    - There may be a slight improvement in HbA_{1c} levels in patients treated with CSII compared with MDI.
    - In the recently completed follow-up study of children treated with insulin pumps, with mean duration of follow-up of 3.5 years, insulin pump therapy compared with a matched cohort using injections was associated with
      - Sustained improvement in glycemic control
      - Reductions of severe hypoglycemia and hospitalization for diabetic ketoacidosis

Meal Plan

- Carbohydrate ingestion is a major determinant of blood glucose concentration.
- Matching the amount of food intake with the appropriate amount of insulin requires knowledge of
  - Onset
  - Peak
  - Duration of action of the various types of insulin available
- No single meal plan has been shown to be superior.
  - As children grow and vary their activity levels, caloric requirements can change significantly.
  - Advice from a dietitian experienced in the management of children with diabetes is necessary.
    - Commonly used meal plans include consistent carbohydrate or exchange diet and carbohydrate counting.
    - Plans require specific education.
    - Patients must be able to assess the nutrient content of foods.
    - Patients must understand how nutrition affects the management of their disease.
- Exchange diet.
  - Patient eats a consistent amount of nutrients at a consistent time of day.
    - Example: 45 g of carbohydrate for breakfast, 60 g for lunch, and 60 g for dinner.

  - Fat and protein may also be prescribed for each meal.
  - The patient is expected to eat according to this pattern each day.
- Foods are categorized according to nutrient content.
  - Foods with equivalent nutrient content can be exchanged for each other to introduce variety.
  - Snacks are usually incorporated depending on the individual patient's needs and preferences.
- Advantages.
  - Nutrient intake is consistent.
  - Allows insulin dosing also to be consistent.
  - Can be used for patients on split-mixed, MDI, or CSII programs.

■ Carbohydrate counting.
- More complex than exchange diet but increasingly popular.
  - Patients must be familiar with the carbohydrate content of each food.
- For each unit of carbohydrate taken, a specific amount of insulin must be given to maintain euglycemia.
  - Typical ratio may be 1 unit of short-acting insulin for each 15 g of carbohydrate eaten.
  - Ratio is adjusted for each patient.
  - Ratio may vary based on time of day for a given individual.
- Advantages.
  - Can be used for patients on an MDI or CSII insulin regimen.
  - Carbohydrate counting allows more flexibility in the timing and content of each meal.
- Caveats.
  - Patients can take more insulin to maintain glycemic control while overeating.
  - Carbohydrate counting must be part of an overall meal plan so that overeating does not contribute to obesity or hyperlipidemia.
  - Carbohydrate counting requires specific education and a motivated patient and family.
- Contraindications.
  - Patients on a split-mixed insulin program.
  - Insulin doses in a split-mixed program cannot easily be adjusted to account for the dietary variability of carbohydrate counting.

Exercise

■ Exercise can be performed safely.
- Children should not be discouraged from participating in sports because of diabetes.
- However
  - Attention to the effects of activity on glucose levels can assist in preventing hypoglycemia during or after exercise.
  - Hypoglycemia may occur if changes are not made in the amount of food eaten or insulin taken.
  - The effect of exercise may be sustained and lead to delayed hypoglycemia.

■ Planned activity: 2 methods of preventing hypoglycemia.
- Reduce the dose of short-acting insulin given at the previous meal.
- A snack can be given just before or during the activity.

■ Unplanned activity.
- A snack is the only option.

■ Blood glucose level
- Should be checked before and after exercise to determine effect of activity on glucose concentrations.
- If activity is prolonged (>45–60 minutes), level should be checked
  - Periodically during the activity
  - Again at night
- Documenting the effect of exercise on the patient's glucose level is the only way to prevent hypoglycemia.

Illness

■ Illness can have a notable effect on blood glucose values.
- Hypoglycemia or hyperglycemia may result.
  - Dependent on illness severity and the amount of food eaten

■ Regardless of food intake, insulin is necessary in health or illness.
- A common error made is the omission of insulin injections because the child is not eating.
- Although the dose may change, some insulin should be given even if the child cannot eat.

■ Practical guidelines can assist in appropriate care during illness and avoidance of hospitalization.
- Never completely omit insulin.
- Monitor and record blood glucose concentrations every 2–4 hours.

- Monitor urine ketone concentrations frequently, even if serum glucose level is not significantly elevated (>250 mg/dL).
  - Some patients with T1D can develop ketosis in the absence of hyperglycemia when ill.
- Encourage adequate hydration.

WHEN TO ADMIT

- Admit when diabetic ketoacidosis is present.
- Consider admitting patients with
  - Newly diagnosed T1D
  - Severe hypoglycemia or dehydration

WHEN TO REFER

- Refer when
  - T1D or T2D is newly diagnosed.
  - A multidisciplinary diabetes program is needed and not available.

FOLLOW-UP

- Monitoring
  - Appropriate insulin dosing cannot be accomplished without adequate blood glucose monitoring.
    - Simply checking glucose concentration is not enough.
    - Glucose values must be recorded in a log and reviewed on a regular basis to determine whether insulin doses need to be adjusted.
  - Frequency.
    - Patients with T1D and some patients with T2D treated with insulin
      - Before meals
      - Bedtime
      - Occasionally at night
    - T2D treated with lifestyle modification or oral agents
      - Less frequent monitoring is required.
    - Additional glucose determinations may be needed during
      - Illness
      - Exercise
      - Symptoms of hyperglycemia or hypoglycemia
  - Home management.
    - Many good home glucose monitors are available.
    - All monitors should be checked periodically for accuracy.
    - Patients should receive training on proper technique.
    - Data from many home glucose meters and insulin pumps can be transferred to a computer to assist in tracking glycemic control.
- Adjusting
  - Adjusting insulin doses is necessary to maintain good glycemic control.
    - Adjustment is based on patterns of blood glucose concentrations recorded in the log.
    - Generally made as a 10% increase or decrease.
  - The purpose of adjustment is to prevent future abnormal glucose levels.
    - Primary care physicians should commonly ask patients to look for a 3-day trend of hyperglycemia before making an adjustment.
    - Example: A patient consistently has glucose values before his or her evening meal that are higher than the goal range.
      - An increase in the short-acting insulin before the noon meal would be made.
  - Many variables cannot be accounted for; therefore
    - Patients should be informed that their blood glucose concentration will not always fall in the reference range.
      - For some people, this circumstance can be discouraging and lead to improper insulin adjustments.
      - For others, lack of education or fear of hypoglycemia leads to improper dose adjusting.
  - Primary care physicians must be clear about the difference between insulin adjustments and supplements.
- Supplementing
  - Used to correct a glucose concentration outside the goal range.
    - The supplement (adding or subtracting insulin) is used to correct the abnormal glucose.
    - The bolus dose of short-acting insulin is used to account for the food that will be eaten at a meal.
  - Example: A patient has a blood glucose level that is below the goal range before breakfast.
    - Insulin would be subtracted from the morning bolus dose of short-acting insulin.
  - Example: Glucose is above the goal range before a meal.
    - Supplemental insulin may be added to the bolus dose of short-acting insulin at that meal to correct the hyperglycemia.

COMPLICATIONS

- T1D and T2D greatly increase the risk of
  - Blindness.
  - Chronic kidney disease.
  - Neuropathy.
  - Cardiovascular disease.
  - Stroke.
  - Risks can be attenuated in adolescents and adults treated with intensive diabetes management.
  - Screening for chronic complications must be performed to intervene early to reverse or slow disease progression.
- Hypoglycemia.
  - Common complication of treatment
    - Blood glucose levels should be checked to confirm symptoms are caused by low blood glucose level.
    - Some symptoms of hypoglycemia are nonspecific.
    - Unnecessary treatment should be avoided.
    - Children <5 or 6 years at the time of diagnosis are
      - At particularly high risk of frequent hypoglycemia, cognitive impairment
  - Mild hypoglycemia
    - Symptoms
      - Shakiness
      - Nervousness
      - Tachycardia
      - Sweating
- Older children are generally able to recognize symptoms.
- Younger children may not be able to recognize or effectively communicate these symptoms.
- Primary care physicians must be responsible for identifying hypoglycemia.
- Parents frequently report unusual behavior and irritability as signs of hypoglycemia in younger children.
- Management of mild hypoglycemia.
  - 10–15 g of carbohydrate will correct the situation.
  - Glucose level should be rechecked in 15–20 minutes to be certain hypoglycemia has resolved.
  - Glucose tablets and gels are available and easy to carry.
  - Some form of carbohydrate should always be available to the patient.
- Severe hypoglycemia.
  - Defined as an episode requiring assistance for treatment
  - Symptoms
    - Neurologic symptoms can include confusion or loss of consciousness.
    - Symptoms markedly increase with lowering of HbA_{1c} level.
- Management of severe hypoglycemia.
  - In an unconscious patient, severe hypoglycemia may be treated with glucagon or intravenous glucose.
  - Training on proper use of glucagon should be provided to individuals caring for the patient (eg, parents, school nurses, older siblings, others).
  - Glucagon is reserved for patients with severe hypoglycemia who cannot ingest carbohydrates.
  - Response is short-lived; as soon as practical, the patient should eat.
  - Nausea frequently accompanies glucagon administration.
- After hypoglycemia treatment, the cause should be considered.
  - If no cause is readily apparent, the insulin dose should be adjusted the next day to avoid additional hypoglycemia.
    - This advice is in contrast to monitoring glucose trends before making adjustments to prevent hyperglycemia.
  - One episode of unexplained hypoglycemia should prompt an insulin adjustment.
  - Less tight glycemic control should be considered for patients with frequent severe hypoglycemia and associated long-term neurologic consequences.
- Diabetic retinopathy.
  - Screening is recommended for all individuals with diabetes.
  - Retinopathy within the first 3 years of diagnosis is unusual for a child.
    - Especially if <10 years
  - Ophthalmologic evaluation for children with T1D.
    - Starts at age 10 years in those who have had T1D between 3 and 5 years
    - Annual follow-up thereafter

- Diabetic nephropathy.
  - Leading cause of chronic kidney disease and need for dialysis.
  - Uncommon in the young patient or the patient with newly diagnosed T1D.
  - Screening should start at age 10 years in children who have had T1D for ≥5 years.
    - Random urine sample to determine the microalbumin to creatinine ratio.
    - Ratio of ≥30 mg/g (albumin to creatinine) is considered outside of reference range, and further testing may be indicated.
    - Because other factors may contribute to albuminuria, including exercise, 2–3 determinations outside of reference range may be needed to confirm the diagnosis.
    - Treatment with an angiotensin-converting enzyme (ACE) inhibitor, titrated to normalization of albumin excretion, should be considered when elevated albumin to creatinine ratio is confirmed on 2 additional specimens from different days over at least 2 months.
    - Girls should be counseled on the teratogenicity of ACE inhibitors.
    - Screening for hypertension should be performed at each routine visit.
    - Children found to have high-normal blood pressure or hypertension should have blood pressure confirmed on a separate day.
      - If consistently elevated to >90th percentile for age, height, and gender, ACE inhibitor therapy is the first-choice treatment.
- Dyslipidemia.
  - Screen for dyslipidemia in children >2 years soon after diagnosis (after glucose control has been established) if there is a family history of hypercholesterolemia or cardiovascular event before age 55 years, or if family history is unknown.
  - If family history is not of concern, first lipid screening can be obtained at puberty (~10 years of age).
  - For children diagnosed with diabetes at or after puberty, consider a fasting lipid profile soon after diagnosis (after glucose control has been established).
  - If lipids are abnormal, annual monitoring is reasonable, with institution of lifestyle changes.
  - If low-density lipoprotein cholesterol values are within accepted levels (<100 mg/dL), repeat lipid profile every 5 years.
- Hyperlipidemia.
  - Screening is recommended at or shortly after initial diagnosis of T1D in all patients.
  - Lifestyle and pharmacologic intervention may be required.
- Autoimmune disorders.
  - Thyroid disease (~17% of patients)
    - Screening should begin at or shortly after diagnosis of T1D.
    - Measurement of sensitive thyroid-stimulating hormone.
    - Annual screening thereafter.
  - Celiac disease
    - Patients with T1D are at risk.
    - Screen by measuring tissue transglutaminase antibodies or endomysial antibodies.
    - Reference total immunoglobulin A concentrations should be documented.

PROGNOSIS

- T1D
  - Fatal disease until the discovery of insulin.
    - Progressive metabolic abnormalities, including ketoacidosis, would eventually lead to death.
    - With the availability of insulin for clinical use in the early 1920s, patients were able to survive the more immediate threat of severe acidosis.
  - Uncorrected severe hyperglycemia and metabolic acidosis can lead to neurologic sequelae.
    - Seizures
    - Coma
  - Antibodies predict progression in high-risk individuals with human leukocyte antigen susceptibility or a family history of diabetes.
    - Islet cell antigens
    - Glutamic acid decarboxylase
    - Insulin
- MODY
  - Clinical course can range from mild to progressive disease with the development of microvascular complications.

PREVENTION

- Recognizing early symptoms of diabetes may help prevent
  - Severe diabetic ketoacidosis
  - Potentially fatal outcomes

- Criteria for screening high-risk children for diabetes[1]
  - Overweight (body mass index >85th percentile for age and sex)
  - *Plus* any 2 risk factors
    - Family history of T2D in a first- or second-degree relative
    - High-risk race or ethnicity (ie, Native American, African American, Latino, Asian American, or Pacific Islander)
    - Signs of insulin resistance or associated conditions
      - Acanthosis nigricans
      - Hypertension
      - Dyslipidemia
      - Polycystic ovarian syndrome
    - Maternal history of diabetes or gestational diabetes
  - Age to initiate screening
    - 10 years
    - Onset of puberty if <10 years
  - Frequency: every 3 years
  - Preferred screening test: serum glucose after an 8-hour fast

REFERENCES

1. Adapted from American Diabetes Association. Standards of medical care in diabetes—2014. *Diabetes Care.* 2014;37 (Suppl 1):S14–S80. Copyright © 2014 American Diabetes Association. Reprinted with permission.
2. Adapted from American Diabetes Association. Diagnosis and classification of diabetes mellitus. *Diabetes Care.* 2012;35 (Suppl 1):S64–S71. Copyright © 2012 American Diabetes Association. Reprinted with permission.

Diaper Rash

DEFINITION

- Most common skin disorder of infancy
- Two groups
  - Rash primarily affecting the diaper area and related to wearing a diaper
  - Rash associated with systemic disorders that may involve the perineum
- Two most common forms
  - Irritant contact dermatitis (ICD)
  - Candidiasis

SIGNS AND SYMPTOMS

- ICD appears on the convexities of the lower abdomen, perineum, buttocks, and proximal thighs with relative sparing of creases (eg, inguinal folds).
- Mild cases: erythema, possibly with scaling.
- More severe cases: superficial erosions.
- Infection with *Candida albicans* typically produces "beefy" red patches that involve convexities and creases.
- Scaling, particularly at the periphery of patches, or satellite papules or pustules may be present.

DIFFERENTIAL DIAGNOSIS

- See **Table 1** and **Table 2** for the differential diagnosis of common and less common forms of diaper rash in infants and toddlers.
  - Infections (herpes simplex infection, molluscum contagiosum, hand-foot-and-mouth disease) and infestations (scabies) may involve the diaper area.
  - Lesions in other areas or systemic symptoms would normally be evident.
- Kawasaki disease.
  - May produce perineal erythema and desquamation during the first week of symptoms.
  - May be the only rash in some patients.
  - Eruption involving the convexities and creases, similar in appearance to toxin-mediated erythemas like scarlet fever.
- Bullae or erosions affecting the diaper area may result from bullous impetigo, burns (including those from non-accidental trauma), senna-containing laxatives, or epidermolysis bullosa.

LABORATORY FINDINGS

- Laboratory tests are not usually needed.
- Tests that may be helpful in identifying the cause of a diaper rash include
  - Potassium hydroxide preparation to demonstrate the pseudohyphae and spores of candidiasis or the hyphae of tinea corporis (A fungal culture might be performed instead.)
  - Mineral oil slide preparation for scabies (Mites, eggs, or fecal material might be observed.)
  - Bacterial culture for *Staphylococcus aureus* organisms
  - Serum zinc level suspicion exists for acrodermatitis enteropathica
    - Other testing required to identify nutritional disorders that produce similar physical findings (eg, essential fatty acid deficiency, kwashiorkor)
  - Skin biopsy if concern exists for Langerhans cell histiocytosis
  - Osseous survey if non-accidental trauma is suspected in a child ≤2 years

IMAGING

- Radiography of the skull and long bones may be helpful for evidence of child abuse.

DIAGNOSTIC PROCEDURES

- Skin biopsy
  - Rarely, may be useful in cases in which the diaper rash is atypical or unresponsive to therapy

TREATMENT APPROACH

- Reduce moisture through frequent diaper changes (every 3–4 hours and after soiling).
- Diaper-free periods are helpful but may not be feasible.
- For soiled perineum, bathe or cleanse with a disposable wipe or washcloth and water.
  - Wipes contain water, an emollient, and surfactants.
    - Safe to use on normal infant skin and damaged skin.
    - Choose a fragrance-free product to help avoid sensitization.
    - Preservatives may induce allergic contact dermatitis but can be difficult to avoid.
- After cleansing, allow skin to dry before diapering.
- Apply zinc oxide paste and petrolatum.
  - Barrier preparation at each diaper change protects skin from moisture.
  - Zinc oxide adheres well to the skin and provides greater protection.
    - May be covered with a thin layer of petrolatum to prevent adherence of zinc oxide to diaper

Table 1. Common Forms of Diaper Rash

Condition	Cause	Clinical Features	Treatment
Seborrheic dermatitis	Cause unknown Associated with sebaceous gland function May represent an inflammatory response to yeasts of the *Malassezia* (*Pityrosporum*)	Begins at 3–4 weeks of age and resolves by the end of first year of life Salmon-pink patches with greasy scale that involve convexities and inguinal creases Involvement of scalp, face, retroauricular creases, umbilicus, or chest may be present.	Skin: topical low-potency corticosteroid or antifungal preparation (eg, nystatin, clotrimazole) Scalp: oil massage and brushing or antiseborrheic shampoo (eg, one containing pyrithione zinc or selenium sulfide)
Bullous impetigo	Infection with *Staphylococcus aureus* that elaborates epidermolytic toxin	Flaccid blisters filled with clear or purulent fluid Blisters rupture rapidly, leaving round or oval crusted erosions with a rim of scale.	Oral antistaphylococcal antibiotic (The agent selected depends on local antibiotic resistance patterns.)
Folliculitis	Infection of hair follicles with *S aureus*	Pustules with surrounding erythema that are centered around hair follicles	Many lesions: oral antistaphylococcal antibiotic (The agent selected depends on local antibiotic resistance patterns.) Few lesions: topical antibiotic (eg, mupirocin, clindamycin, retapamulin) Bleach baths may be useful for patients with persistent/recurrent infections.
Intertrigo	Rubbing of apposed skin surfaces complicated by heat and moisture	Erythema and superficial erosions located in the inguinal creases May become secondarily infected with *Candida* species or *Streptococcus pyogenes,* less commonly *S aureus*	Absorbent powder (to reduce moisture and friction) Antifungal preparation (if candidal infection) or antibiotic (if streptococcal infection)
Jacquet erosive diaper dermatitis	Multiple factors, including moisture, friction, enzymes in stool Considered a variant of infant dermatitis	Well-defined shallow ulcers or ulcerated nodules	Topical low-potency corticosteroid twice daily and barrier preparation at all diaper changes

Adapted from American Academy of Pediatrics. *Pediatric Dermatology: A Quick Reference Guide.* 3rd ed. Mancini AJ, Krowchuk DP, eds. Elk Grove Village, IL: American Academy of Pediatrics; 2016.

Table 2. Less Common Forms of Diaper Rash

Condition	Cause	Clinical Features	Treatment
Psoriasis	Unknown	Erythematous scaling papules or plaques (Scaling of the scalp and umbilicus may be present.) Lesions in the diaper area often lack scale characteristic of lesions located elsewhere. May be difficult to distinguish from seborrheic dermatitis	Topical emollient and topical low-potency corticosteroid
Allergic contact dermatitis (ACD)	Allergy to diaper components (eg, dye, adhesive)[a,b] Senna-containing laxative (may be allergic or irritant)[c] Wipes (preservative)[d]	Diaper: erythematous patch, possibly with scaling or lichenification. Rash located at site of contact with offending agent; often the hips (adhesive) or diaper margin (dye). Senna: bullae and erosions that may mimic findings in child abuse Wipes (preservative): persistent or recurrent eruption in the perineum or on the buttocks	Diaper: Change diaper variety/consider testing for ACD; apply topical low-potency corticosteroid. Senna: Manage as wound with topical antibiotic; avoid senna-containing laxatives. Wipes: Change wipe variety/consider testing for ACD; apply topical low-potency corticosteroid.
Acrodermatitis enteropathica	Autosomal-recessive disorder Defective transport protein causes impaired zinc absorption.	Often begins when infants are weaned from human to cow's milk formula Scaling erythematous eruption located around the mouth and in the diaper area Infants may have sparse hair, diarrhea, or failure to gain weight.	Oral zinc supplementation Topical low-potency corticosteroid
Langerhans cell histiocytosis	Rare disorder; Langerhans cells (antigen-processing cells in the skin) accumulate in skin or other organs.	Lesion types: vesicles or pustules (often with a hemorrhagic crust); erythematous, orange, or yellow-brown papules or nodules; petechiae; erosions (in the diaper area) Areas affected: scalp, palms and soles, skinfolds, diaper area Other features: Affected infants may have hepatosplenomegaly.	Refer to pediatric dermatologist or pediatric oncologist for evaluation.

Table 2 (*continued*)

Condition	Cause	Clinical Features	Treatment
Congenital syphilis	Intrauterine infection with *Treponema pallidum*	Symptoms: rash, bloody diarrhea, rhinorrhea, irritability, pain with movement (Parrot pseudoparalysis) Skin lesions: condyloma lata (ie, flat-topped papules and plaques located in the diaper area or at the angles of the mouth), scaling copper-colored papules and plaques on the trunk and extremities or vesicles and bullae	Consult with a pediatric infectious diseases specialist about evaluation and therapy.

Adapted from American Academy of Pediatrics. *Pediatric Dermatology: A Quick Reference Guide.* 3rd ed. Mancini AJ, Krowchuk DP, eds. Elk Grove Village, IL: American Academy of Pediatrics; 2016.

[a] Smith WJ, Jacob SE. The role of allergic contact dermatitis in diaper dermatitis. *Pediatr Dermatol.* 2009;26(3):369–370

[b] Alberta L, Sweeney SM, Wiss K. Diaper dye dermatitis. *Pediatrics.* 2005;116(3):e450–e452

[c] Smith WA, Taintor AR, Kos L, Drolet B. Senna-containing laxative inducing blistering dermatitis in toddlers. *Arch Dermatol.* 2012;148(3): 402–404

[d] Chang MW, Nakrani R. Six children with allergic contact dermatitis to methylisothiazolinone in wet wipes (baby wipes). *Pediatrics.* 2014;133(2):e434– e438

- Active ingredients in many combination products, along with beeswax, lanolin, mineral oil, olive oil, and other agents.

SPECIFIC TREATMENTS

- Corticosteroids.
  - For moderate or severe ICD, a low-potency topical corticosteroid (eg, hydrocortisone 1% or 2.5%) may be applied twice daily.
  - Avoid using more potent preparations.
  - Absorption is enhanced by occlusion of the perineum by the diaper and the thinness of the epidermis, increasing the likelihood of adverse effects.
    - Locally (eg, atrophy, striae)
    - Systemically (eg, Cushing syndrome)
- Candidiasis.
  - If physical examination suggests candidiasis or if ICD has been present >72 hours and is not improving with standard treatment
    - Use nystatin or an imidazole (eg, clotrimazole, miconazole, ketoconazole).
    - Imidazoles may be a more convenient choice in view of twice-daily dosing.
    - If both a topical corticosteroid and an imidazole are used, select an alternating application schedule.
    - Apply a barrier preparation at all diaper changes where the topical corticosteroid or antifungal is not being used.
- In infants with skin of color, inflammation caused by ICD or other forms of diaper dermatitis may cause hypopigmentation.
  - Parents should be advised that this is temporary but may require several months to resolve.

WHEN TO REFER

- If an infant fails to respond to appropriate therapy, to consider alternate diagnoses and possibly perform skin biopsy.
- If non-accidental trauma is suspected.
- If Langerhans cell histiocytosis is considered, refer to a pediatric dermatologist or pediatric oncologist.
- Consultation with a pediatric infectious disease specialist is warranted if an infant is suspected of having congenital syphilis.

PREVENTION

- Preventive measures.
  - Frequent diaper changes
  - Appropriate skin cleansing promptly after soiling

- Application of barrier preparation, particularly for infants who experience recurrent episodes of diaper dermatitis

■ Because going diaper-free is unacceptable, parents must choose between disposable and cloth diapers.
- Issues that influence this decision
  - — Effectiveness
  - — Prevention of diaper dermatitis
  - — Cost
  - — Ecologic effect
- Cloth diapers
  - — Increasing popularity likely reflects, in part, satisfaction with their performance.
  - — Depending on the brand, these diapers use a cloth insert (to enhance absorbency) and a breathable waterproof cover.
  - — Some varieties use a flushable inner liner for fecal material, eliminating the need to rinse before placing in the diaper pail.
  - — Less expensive than disposables, especially if the family does the laundering.
  - — Can be used for more than a single baby.
  - — Washing requires water, energy, detergent, and human effort.
  - — Reusable diaper use resulted in 570 kg of carbon dioxide equivalents (assuming average washer and dryer use).
    - ■ Could be reduced by 40% by washing diapers in fuller loads, line drying, and using diapers for a second child
- Disposable diapers
  - — Convenient but comparatively more expensive
    - ■ A family might spend $2,500 or more by the time a child is toilet trained.
    - ■ Biodegradable diapers may cost $3,500.
  - — Environmental effects
    - ■ Nonbiodegradable disposable diapers make up 1% to 2% of landfills.
    - ■ A child using 2006-type disposable diapers for 2½ years contributed a global warming effect of ~550 kg of carbon dioxide equivalents.

DEFINITION

- Diarrhea
  - Increased stool frequency
  - Stools with increased water content
- Steatorrhea
  - Excess fat in the stool

HISTORY

- During initial evaluation, establish
  - Length of illness
  - Characterization of stools
    - Frequency
    - Looseness (watery vs mushy)
    - Presence of gross blood
  - Oral intake
    - Diet
    - Quantity of fluids and solids taken
  - Presence of vomiting
  - Associated symptoms
    - Fever
    - Rash
    - Arthralgia
  - Urine output
    - Frequency
    - Qualitative amount
  - Possible exposure to diarrheal illness

PHYSICAL EXAMINATION

- Determine hydration status.
  - Mild dehydration: 3% in infants and 5% in older children
    - Dry mouth
    - Absence of tears
  - Moderate dehydration: 6% in infants and 10% in older children
    - Dry mouth
    - Absence of tears
    - Sunken eyes
    - Sunken fontanel
    - Poor skin turgor
  - Severe dehydration: >9% in infants and ≥15% in older children
    - Shock
- Assess body weight.
  - A recorded weight is essential.
    - Can be compared with previous weights
    - Can be used to reevaluate the child's state of hydration during the illness
  - Infants should be weighed at least daily.
- Assess
  - Vital signs
  - Capillary refill
  - Alertness
  - In infants, vigor of suck
- Measurement of stool output
  - If urine is collected in a urine bag, diapers can be weighed before and after stools to give an accurate measure of stool output.

DIFFERENTIAL DIAGNOSIS

Steatorrhea

- Cystic fibrosis
- Celiac disease
- Pancreatic insufficiency, as detected by measurement of stool elastase or serum trypsinogen
- Congenital pancreatic insufficiency with cyclic neutropenia (Shwachman-Diamond syndrome)
- Intestinal lymphangiectasia
- Abetalipoproteinemia
- Transient steatorrhea following acute enteritis

Acute Diarrhea

Neonates

- Neonates with acute diarrhea must be considered differently from older infants and children.
  - Lower tolerance to associated fluid shifts
  - Greater likelihood of severe infection or congenital anomaly
- Signs of necrotizing enterocolitis should raise concern.
  - Gastric retention (frequently bilious).
  - Distention.
  - Occult or bright-red blood in the stool.
  - More common in preterm neonates.
  - The presence of pneumatosis intestinalis (gas in the portal vein or free intraperitoneal gas seen on abdominal radiographs) supports the diagnosis.
- Epidemics of diarrhea associated with rotavirus; enteropathogenic *Escherichia coli; Salmonella;* and other organisms, including *Klebsiella*, have been reported in nurseries.
- Onset of diarrhea associated with initial feedings.
  - Consider congenital digestive defects, especially sugar intolerance.
- Hirschsprung disease.
  - May produce acute diarrhea and enterocolitis in the neonatal period
  - Should be considered, especially in the neonate who has not passed meconium in the first 24 hours

- Bloody diarrhea
  - May result from cow's milk or soy protein intolerance.
  - May develop as early as the first few days of life.
  - Resolution and exacerbation on removal and reintroduction of cow's milk or soy formula, as well as an atopic family history, are clues to the diagnosis.

Infants and Children

- Enteric infection
  - Transmission is commonly by food, water, person-to-person spread, and exposure to animals.
  - Child care centers are likely sites for spread.
  - Viral enteritis—typically without blood in stool.
    - Rotavirus
    - Norovirus
      - One of the most common pathogens associated with food-borne illness and epidemics
      - Epidemics reported on cruise ships and college campuses
    - Adenovirus
    - Cytomegalovirus
      - Especially in immunocompromised children
  - Bacterial enteritis—can be bloody (dysentery) or without blood in stool.
    - *Salmonella*
      - Common cause of food-borne illness, especially from poultry and eggs.
      - Symptoms of dysentery (tenesmus, urgency, lower abdominal pain) may be less marked than with other pathogens.
    - *Shigella*
      - Often associated with bloody, foul-smelling stools.
      - Patients may appear severely ill and may have meningismus or seizures.
      - Can cause hemolytic uremic syndrome (HUS).
    - *E coli*
      - Produces diarrhea by several pathogenic mechanisms.
      - Enteroadherent, enteroinvasive, enterohemorrhagic, and enteroaggregative forms can be associated with blood in the stool.
      - Enterohemorrhagic *E coli* (especially serotype O157:H7) is the most common cause of HUS in children.
    - *Campylobacter*
      - Common cause of food-borne illness, especially from poultry and eggs
      - Associated with up to 40% of cases of Guillain-Barré syndrome
      - Can cause reactive arthritis
    - *Yersinia enterocolitica*
      - Relatively uncommon in the United States
  - Bacterial-toxin induced diarrhea.
    - *Clostridium difficile* toxin
      - The cause of most cases of pseudomembranous colitis
      - May be associated with chronic childhood diarrhea in the absence of colitis
    - *E coli* enterotoxin C
      - In older infants and children, associated with watery stools
      - No evidence of mucosal invasion (ie, no high fever or blood in the stool)
    - *Vibrio cholerae* enterotoxin
      - Profuse, painless, watery diarrhea
      - Major epidemics through spread by contaminated water
      - Spread also by contaminated seafood
  - Parasitic infection
    - *Giardia intestinalis*
      - Watery diarrhea with intestinal gas and crampy abdominal pain
      - Has been implicated in child care center outbreaks
    - *Entamoeba histolytica*
      - Produces a picture of acute colitis
    - *Cryptosporidium*
    - *Cyclospora*
    - *Dientamoeba fragilis*
    - *Blastocystis hominis*
- Parenteral diarrhea
  - Diarrhea in association with extraintestinal infections, most notably otitis media and pyelonephritis.
  - The mechanism is obscure.
  - Associated viral enteritis in some cases of otitis media.
  - Certain antibiotics, especially ampicillin, have been associated with transient diarrhea.
  - Less common but of greater danger is antibiotic-associated pseudomembranous colitis.
    - May occur acutely or as a more chronic illness lasting 1–2 months

- Food-borne spread of organisms or toxins
  - Improperly prepared poultry and eggs are the major source for campylobacteriosis and salmonellosis.
  - The major source for *E coli* O157:H7 infection is ground beef.
  - Preventive measures include
    - Safe food-handling practices
    - Pasteurization of in-shell eggs
    - Irradiation of ground meat and raw poultry
  - Explosive diarrhea after ingesting seafood is likely from infection with *Vibrio* species.

Chronic Diarrhea

- Many causes of chronic diarrhea may appear at any time in childhood.
- Dividing the causes of chronic diarrhea between infancy and older childhood is arbitrary because the groups overlap but is helpful in guiding initial evaluation.

Infants

- Chronic nonspecific diarrhea (toddler's diarrhea)
  - The most common persistent diarrhea during the latter half of the first year and second year of life.
  - No apparent cause.
  - Sometimes follows an apparent acute gastroenteritis (postinfectious irritable bowel).
  - Child appears healthy and thriving, with normal growth parameters.
  - Loose stools during the day; typically not overnight.
  - A stool pattern rather than a pathologic state.
  - Minimal or no workup needed.
- Protracted diarrhea of infancy
  - Poorly understood
  - Previously called *intractable diarrhea of infancy*
  - Probably represents the final pathway for multiple causes
    - Gastrointestinal (GI) infections
    - Food intolerances
  - Defined somewhat arbitrarily as occurring in infants <3 months and persisting >2 weeks
  - In the past, associated with high mortality from irreversible diarrhea and related malnutrition
    - Outcome has improved markedly with the advent of elemental diets and total parenteral nutrition (TPN).
  - Now rare and related to more specific causes, such as microvillus inclusion disease
- Hirschsprung disease
  - Accounts for ~25% of intestinal obstructions in newborns.
    - Almost invariably fail to pass meconium early
    - Persistent obstipation and recurrent abdominal distention
    - Usually have a history of absence of stools in the first 24 hours of life
  - These features may be overlooked, and neonates may subsequently have chronic diarrhea.
  - The diarrhea is secondary to enterocolitis.
    - Enterocolitis can be a surgical emergency that demands rapid diagnosis and treatment.
  - Newborns with Hirschsprung disease require decompression colostomy to remove risk of perforation of the colon.
- Malabsorption syndromes (Diarrhea is often associated with steatorrhea and growth failure.)
  - Cystic fibrosis
    - Although cystic fibrosis is thought of primarily as a respiratory disease, some infants and children have malabsorption and little history of respiratory symptoms.
    - Patients typically have voracious appetites.
    - Diagnosis must be confirmed by sweat electrolyte studies or genetic testing.
  - Celiac disease (gluten-sensitive enteropathy)
    - Much more common than previously recognized.
    - In infancy, celiac disease becomes apparent one to several months after introduction of gluten-containing products (eg, wheat, rye, barley) into the diet.
    - Diagnosis should be confirmed by small-bowel biopsy.
    - *Giardia* infection can produce small-bowel malabsorption that mimics celiac disease.
  - Carbohydrate (monosaccharide or disaccharide) intolerance
    - Usually secondary to other GI disorders.
    - Extent of symptoms varies in response to quantity of the offending sugar in the diet.
    - Age at presentation varies with age at which the sugar is introduced into the diet.
  - Congenital deficiency of trypsinogen, the zymogen precursor of the pancreatic protease trypsin (very rare)

- Recently described as congenital, autosomal-recessive disorder of chronic malabsorption and diarrhea characterized by lack of intestinal enteroendocrine cells from a mutation in the gene *NEUROG*
  - Associated with glucose intolerance

■ Infection
- Acute viral or bacterial enteritis may be the initiator of chronic diarrhea, especially in infants.
  - May be difficult to prove if the infection is no longer active at the time of evaluation for chronic diarrhea
- Infections at distal sites can initiate diarrhea—particularly common is urinary tract infection.
- *Candida.*
  - Rare cause of diarrhea in immunocompetent individuals.
  - Incidental finding of *Candida* is so common that the clinician must be cautious before identifying it as the cause of diarrhea.
  - Dramatic response to treatment for *Candida* would support this diagnosis.
- *Salmonella* infection may be associated with persistent diarrhea in infants.
  - More commonly associated with a prolonged, asymptomatic carrier state
- *Y enterocolitica* enteritis has been associated with a chronic relapsing diarrhea, although not commonly in the United States.
  - The microbiology laboratory must look specifically for this organism or it will be missed.
- *Campylobacter* enteritis also may have a protracted course.
- Persistence of rotavirus or enteric adenovirus excretion has been identified in immunocompromised individuals.
  - Rarely, rotavirus may be present in stool of immunocompetent children for a prolonged period after severe gastroenteritis.
- *C difficile* toxin.
- Parasites.
  - *G intestinalis*
    - Principal parasitic cause of diarrhea in United States
    - May be associated with watery diarrhea and crampy abdominal pain
    - May be epidemic, especially in child care centers
  - *Cryptosporidium*
    - Causes diarrhea in immunocompetent individuals
  - *Cyclospora*
  - *B hominis*
  - *E histolytica*
    - Amebic dysentery may be indistinguishable clinically from the colitis of inflammatory bowel disease (IBD).
  - *D fragilis*

■ Food allergy
- 6%–8% of children have dietary protein hypersensitivity during the first 5 years of life.
- Hypersensitivity to cow's milk protein is most common.
- Symptoms resolve by 3 years of age in 85% of children.
- Consider in an infant with chronic diarrhea with any of the following manifestations:
  - Occult or gross blood in the stool (colitis)
  - Protein-losing enteropathy
  - Peripheral eosinophilia
  - Other extraintestinal manifestations of allergy (eg, eczema, hives, or asthma)
- Most food allergic reactions include immediate GI hypersensitivity.
  - Nausea
  - Abdominal pain
  - Vomiting within 1–2 hours
  - Diarrhea in 2 hours
- Implicated food proteins include
  - Milk
  - Egg
  - Peanut
  - Soy
  - Cereal
  - Fish
- Eosinophilic (allergic) gastroenteropathy.
  - Characterized by infiltration of the stomach and intestine with eosinophils and often a peripheral eosinophilia.
  - Symptoms include vomiting, abdominal pain, growth failure, and diarrhea (often with gross blood).
  - May respond to elimination diet, but corticosteroid treatment may be necessary.
  - Non–immunoglobulin E (IgE)–mediated hypersensitivity food protein-induced enterocolitis syndrome can occur at any age but appears most commonly in the first year of life.

- Diet-induced proctitis.
  - Gross blood in stool.
  - Diarrhea in the first few days to months of life.
  - Symptoms usually resolve within 72 hours with removal of the offending food allergen.
  - Bloody diarrhea can develop in some infants while they are nursing.
    - Resolution when cow's milk is removed from the mother's diet or when a protein hydrolysate formula is substituted for nursing suggests an allergic basis.

- Short-bowel syndrome
  - Chronic malabsorption and diarrhea follow extensive resection of the small intestine.
  - Begins most commonly in the newborn period in association with necrotizing enterocolitis or congenital anomaly involving small intestine (eg, gastroschisis, intestinal atresia, malrotation with secondary midgut volvulus).
  - TPN may be required for the first several years of life.
- Intestinal lymphangiectasia
  - Protein-losing enteropathy
  - Steatorrhea
  - Lymphocytopenia
  - Chronic diarrhea
  - Sometimes, hypogammaglobulinemia and hypoalbuminemia, usually with peripheral edema
  - Primary intestinal lymphangiectasia
    - Appears to be a developmental anomaly of unknown origin
    - Often associated with lymphatic abnormalities of the extremities
  - Secondary lymphangiectasia may result from
    - Chronic volvulus secondary to malrotation with malfixation of the bowel
    - Constrictive pericarditis
    - Tumor
    - Lymphatic malformation
    - Elevated right atrial pressure associated with the Fontan procedure for congenital heart disease
    - Any other factor that leads to obstruction of intestinal lymphatic flow
  - The diagnosis is suggested by
    - History of chronic diarrhea and poor growth
    - Peripheral edema
    - Hypoalbuminemia
    - Hypogammaglobulinemia
    - Lymphocytopenia
- Acrodermatitis enteropathica
  - Rare familial disease.
  - Typically appears when breastfed infants are weaned.
  - Associated with a zinc deficiency, possibly secondary to malabsorption.
  - Mutation of a gene that encodes zinc-transporter protein has been identified in this condition.
  - Nutritional zinc deficiency (eg, TPN without zinc supplementation, cystic fibrosis) may produce a syndrome similar to acrodermatitis enteropathica.
- Factitious diarrhea
  - More common than pediatricians recognize.
  - Laxative abuse may be suspected when an infant has persistent diarrhea that does not seem to fit any known pattern.
    - Surreptitious administration of laxative to an infant demonstrates the caregiver's psychosocial dysfunction.
  - Stool osmolality well below 290 mOsm/L can occur only by surreptitious dilution of stool with water.
  - Factitious diarrhea occurs among teenaged girls who take laxatives surreptitiously to lose weight.
- Hormonal
  - Adrenal insufficiency
    - Adrenogenital syndrome
    - Adrenal hemorrhage
  - Hyperthyroidism
    - Congenital thyrotoxicosis
  - Vasoactive intestinal polypeptide–secreting tumors of the pancreas (rare)
  - Ganglioneuroma and ganglioneuroblastoma
    - Associated with chronic secretory diarrhea.
    - Usually abdominal but also reported in the mediastinum.
    - Catecholamine-secreting, but prostaglandins or vasoactive intestinal polypeptide may be the mediator of the diarrhea.
    - Diarrhea usually resolves abruptly when a tumor is found and is completely excised.
- Immunodeficiency states
  - Chronic parasitic and viral (cytomegalovirus, adenovirus, rotavirus) infections can cause diarrhea in patients with immunodeficiency.
  - AIDS.
    - A major cause of immunodeficiency in childhood.
    - Its first manifestation may be diarrhea.

  - In addition to the organisms the clinician usually considers in individuals with persistent diarrhea (especially *Giardia*), cytomegalovirus, *Mycobacterium avium-intracellulare* complex, *Cryptosporidium parvum, Cystoisospora belli*, and *Enterocytozoon bieneusi* must also be considered.
  - Astrovirus, calicivirus, and adenovirus have been associated with diarrhea in HIV-infected individuals and may be more important than rotavirus as agents of AIDS diarrhea.
  - HIV may be a primary pathogen in the bowel of these patients as well.
  - Lactose intolerance occurs commonly in individuals with AIDS, presumably as a result of injury to small-bowel mucosa.
  - Pancreatic insufficiency with steatorrhea also has been noted in these patients.
- Inborn disorders of immunity.
  - Severe combined immunodeficiency
  - Wiskott-Aldrich syndrome
- Late-onset, variable hypogammaglobulinemia.
- Pure T-cell abnormalities (DiGeorge syndrome and other T-cell deficiencies).
- Selective IgA deficiency.
  - Patients have an increased risk of celiac disease.
- Chronic granulomatous disease of childhood.
  - Perianal fistulas or gastric outlet obstruction may be seen.
  - May initially be mistaken for Crohn disease.
- Children who have received organ transplants.
  - Consider the full range of enteric infections associated with immunosuppression.
  - Tacrolimus toxicity.
  - Lymphoproliferative disease.
- Graft-versus-host disease.
  - Common cause of diarrhea in bone marrow transplant recipients

■ Autoimmune enteropathy
- Chronic diarrhea beginning in the first year of life.
- Often associated with failure to thrive.
- Extraintestinal autoimmune disorders (eg, diabetes mellitus, arthritis, thrombocytopenia, hemolytic anemia) are common.
- Rule out celiac disease, food allergy, and GI infection.
- Response to immunosuppressive therapy confirms the diagnosis.

■ Immunodysregulation, polyendocrinopathy, enteropathy, X-linked syndrome

■ Idiopathic intestinal pseudo-obstruction
- A group of rare disorders characterized by widespread GI dysmotility.
- In early infancy
  - Vomiting and diarrhea.
  - Diarrhea may alternate with constipation.
- In older children
  - More insidious presentation.
  - A long history of constipation may precede the onset of diarrhea.
- Intermittent or constant abdominal distention.
- Roentgenographic findings of bowel dilation with disordered motility.
- Urinary bladder dysfunction often is present.
- Bacterial overgrowth is an important cause of diarrhea in this disorder.

■ Microvillus inclusion disease
- Familial enteropathy.
- Present from birth.
- Causes severe intractable secretory diarrhea with malabsorption.
- Although rare, it is the most common cause of intractable diarrhea in the neonatal period.
- Several families have been identified with >1 child with this disorder.

■ Tufting enteropathy
- Name derives from typical tufted configuration of intestinal mucosal epithelium on light microscopy
- Not present at birth—onset of chronic watery diarrhea in first few months of life

■ Congenital disorders of electrolyte absorption
- Congenital chloride-losing diarrhea and congenital sodium-secretory diarrhea (very rare)
  - Autosomal recessive
  - Associated with maternal polyhydramnios

■ Congenital disorders of glycosylation
- Exhibit in the first year of life, often with multisystem dysfunction.
- Hepatic, neurologic, cardiac, and optic manifestations.
- Can be associated with chronic diarrhea or severe protein-losing enteropathy, or both.
- Screening for this diagnosis has been performed with serum transferrin isoelectric focusing.

■ Lactase deficiency

■ Disaccharide intolerance

■ Chronic constipation with overflow diarrhea

- Monosaccharide intolerance
- Post-enteritis bile acid malabsorption
- Congenital deficiency of enterokinase
- Neural crest tumor and carcinoid
- Intestinal stricture or blind loop
- Pancreatic insufficiency with neutropenia
- Trypsinogen or enterokinase deficiency
- Abetalipoproteinemia
- Ileal bile salt receptor defect

Newborn of a Drug-Addicted Mother

- Diarrhea may be a prominent manifestation of neonatal drug abstinence syndrome.
- This diagnosis should be considered in newborns with persistent diarrhea, especially when other symptoms of neonatal drug withdrawal are present.

Older Children

- Older children are seen with chronic diarrhea less often than infants and young children.
  - Older children are more likely than younger children to have serious underlying disease.
  - The association of poor growth, weight loss, or other systemic manifestation makes serious underlying disease more likely.
  - Many of the causes seen in infancy may also first manifest later in childhood.
- Irritable bowel syndrome.
  - Alternating diarrhea and constipation.
  - Recurrent crampy abdominal pain is common.
  - Important to rule out late-onset lactose intolerance, fructose or sorbitol ingestion, IBD, and celiac disease.
- IBD: Crohn disease or ulcerative colitis.
  - Presentation so variable that IBD should be considered in any older child with chronic diarrhea.
  - Evidence of systemic inflammation (fever, weight loss, leukocytosis), blood in stools (gross or occult), perianal disease, anemia, abdominal pain, or extraintestinal manifestations (arthritis, arthralgia, erythema nodosum) make IBD more likely.
  - Growth failure can precede or occur with other symptoms.
  - Elevated sedimentation rate is suggestive, but up to half of patients have normal erythrocyte sedimentation rate.
- Chronic constipation.
  - Chronic constipation with overflow incontinence can be mistaken for diarrhea.

Diarrhea That Usually Occurs Without Blood in Stool

- Viral enteritis: rotavirus, orbivirus, noroviruses, other caliciviruses, enteric adenovirus, astrovirus, *Sapovirus* species
- Enterotoxin: *E coli, Klebsiella* organisms, *Clostridium perfringens*, *Staphylococcus* organisms, *Bacillus cereus*, *Vibrio* species
- Parasitic: *Giardia, Cryptosporidium*, *Cyclospora, D fragilis*, and *B hominis*
- Extraintestinal infection: otitis media and urinary tract infection
- Antibiotic-induced and *C difficile* toxin (without pseudomembranous colitis)

Diarrhea That Commonly Is Associated With Blood in Stool

- *Shigella, Salmonella*, and *Campylobacter* organisms
- *C difficile* toxin–associated pseudomembranous colitis
- *Y enterocolitica*
- Invasive *E coli*
- Gonococcus (venereal spread)
- Enteroadherent *E coli*
- Enteroaggregative *E coli*
- *Aeromonas hydrophilia*
- *Plesiomonas shigelloides*
- Cytomegalovirus (especially in immunocompromised individuals)
- *E histolytica* (amebic dysentery)
- *Trichuris trichiura* (whipworm)
- HUS (enterohemorrhagic *E coli*—*E coli* O157:H7 and other Shiga toxin-producing *E coli*)
- Henoch-Schönlein purpura
- Ulcerative or granulomatous colitis (acute presentation)
- Necrotizing enterocolitis (neonates)

LABORATORY EVALUATION

- Stool evaluation: Test for viral etiology when available, culture, ova and parasites, smear for white blood cells, *C difficile* toxin assay, occult blood, and reducing substances.
  - Leukocytes or gross blood in stool usually indicates colonic inflammation, infectious or noninfectious.
  - Occult blood in stool suggests loss of blood across the mucosa anywhere in the GI tract.
  - Stool pH is not a good measure of diarrhea's effect on total body acid-base balance.

- If stool concentration of sodium and potassium minus chloride is greater than plasma bicarbonate, the patient is losing bicarbonate.
- Culture stool if blood or leukocytes are noted in the stool and the child appears ill.
- For a child with chronic diarrhea who has been fed recently, the presence of reducing substance or an acid stool pH (<5.3) suggests carbohydrate malabsorption.

- If child is lethargic or has had a seizure
  - Culture for sepsis.
  - Measure serum urea nitrogen, serum electrolytes, and glucose levels.
  - Examine and culture cerebrospinal fluid.
- Polymorphonuclear leukocytes.
  - Usually account for at least 60%–80% of the cells.
  - The presence of only occasional cells is considered a negative finding.
  - Leukocytes are found in high numbers, frequently in sheets, in infectious and noninfectious colitis.
  - Absence of leukocytes in grossly bloody diarrheal stool occurs with enterohemorrhagic *E coli* infection but should also direct attention to such entities as intussusception and Meckel diverticulum when these diagnoses seem clinically appropriate.
  - Amebic colitis may not be associated with leukocytes in the stool, although the trophozoites and numerous red blood cells may be visible on a saline wet mount preparation of the stool.
  - Invasive bacterial diarrhea frequently is associated with a peripheral blood leukocytosis.
- Complete blood cell count.
- Urinalysis.
- Urine-specific gravity and volume.
  - May be deceptive because of poor concentration by the kidneys in the presence of malnutrition and total body hypokalemia
- Serum urea nitrogen and serum electrolyte levels if hydration status is in question.
  - Hypernatremia indicates more severe dehydration than suggested on physical examination.
- Endomysial IgA or tissue transglutaminase antibody may be useful in assessing adequacy of gluten-free diet or evaluating adherence to diet.

IMAGING

- Flat-plate radiograph of the abdomen.
  - In Hirschsprung disease, may show a dilated colon with absence of air in the rectum.
  - Toxic megacolon may also be seen in infectious colitis or in chronic IBD in infancy.
  - Air-fluid levels throughout the bowel.
    - Common in infants with gastroenteritis
    - Not helpful in defining a cause
- Barium enema under low pressure in the unprepared patient may show the narrow distal segment of rectum in Hirschsprung disease.
  - Delayed radiograph (24–48 hours after barium enema) may show the transition zone.
- In suspected IBD, after laboratory studies and stool assay, consider
  - Conventional contrast radiography
  - Computed tomography of abdomen and pelvis
  - Magnetic resonance enterography

DIAGNOSTIC PROCEDURES

- Protracted diarrhea of infancy
  - Small-bowel biopsy specimen may show patchy villous shortening with a decreased villus to crypt ratio and marked inflammation, as well as a damaged surface epithelium.
    - However, the results of the small-bowel biopsy also may be normal.
  - Similarly, a rectal biopsy specimen may show evidence of inflammation, including crypt abscesses, or it may be normal.
  - Presence or absence of these biopsy findings may not correlate with severity of the clinical syndrome.
  - Several stools should be collected for culture, examination for parasites, and *C difficile* toxin assay when indicated.
    - Blood and urine cultures should also be ordered.
- In suspected IBD
  - Consider endoscopy and biopsy of upper GI tract and colon.
  - Stool assay for calprotectin.
- Stool antigen testing is sensitive for
  - *Giardia*
  - *Cryptosporidium*

TREATMENT APPROACH

- Guidelines for rehydration
  - The most recent World Health Organization recommendation is for a lower osmolarity (245 mOsm/L) solution, containing 75 mEq/L sodium and 75 mmol/L glucose.
  - Continuing regular feedings with supplemental oral rehydration solution (ORS) is generally tolerated and thought to lead to quicker recovery.
  - Vomiting is usually not a contraindication to oral rehydration.
- Fluid and electrolyte management
  - Commercial ORS provides more sodium and lower carbohydrate concentration than traditional clear liquids.
    - Electrolyte content in diarrheal stool varies widely.
      - Fecal sodium levels range from 40–100 mEq/L, occasionally as high as 150 mEq/L.
      - Highest concentrations occur in secretory diarrheas, such as cholera.
      - In rotavirus diarrhea, fecal sodium concentration typically is 20–40 mEq/L.
    - Human milk contains low concentrations of sodium (6–7 mEq/L).
  - Supplemental ORS should be used when diarrhea is persistent or severe and to replace diarrheal losses in infants.
    - Infants with diarrhea can usually drink large volumes of salty-tasting liquids ad lib appropriate for the stool output.
    - Liquids can be offered ad lib.
    - Smaller volumes per feeding may be better tolerated when diarrhea is accompanied by vomiting.

SPECIFIC TREATMENT

Acute Gastroenteritis

- Cornerstone of treatment in acute gastroenteritis is good fluid and electrolyte management (**Box 1**).
- Indications for medications in the treatment of acute gastroenteritis in infants and children are limited.
  - There is no apparent rationale for medications that slow gut motility (diphenoxylate, loperamide, and anticholinergics).
    - Slowing intestinal transit with drugs may allow greater mucosal contact with pathogens and thereby permit local mucosal invasion.
  - Bismuth subsalicylate, which may decrease the duration of diarrhea, has been shown to be a safe adjunct to oral rehydration but is not used routinely.
- Antibiotics are useful in specific situations.
  - *Shigella* dysentery.
  - *Yersinia* or *Campylobacter* gastroenteritis.
    - *Campylobacter* infection must be identified very early for antibiotics to shorten the illness.
  - Pseudomembranous colitis.
  - *Salmonella* infections in infants <6 months.
  - *Salmonella* infections in older patients who have enteric fever, typhoid fever, or complications of bacteremia.
  - For the individual patient, the presence of an *E coli* serotype previously labeled enteropathogenic correlates poorly with the presence of diarrhea and is not alone an indication for antibiotic treatment.
- *Lactobacillus* or other probiotics may be useful to prevent infectious diarrhea but are probably not effective as treatment.

Rotavirus

- The current approach to treatment is to restart the previous full-strength formula and solids early after the onset of diarrhea.
- If diarrhea recurs on the introduction of lactose-containing formula, the child may have transient lactose intolerance.
  - In this situation, a lactose-free formula should be offered.
  - Transient lactose intolerance usually lasts only ≤1 week but can, at times, persist for months.

Severe Dehydration and Shock

- Rapid intravenous administration of 10–20 mL/kg of isotonic fluid or colloid is required initially.
- May need to be repeated early.

Chronic Diarrhea

Infants and Children: Chronic Nonspecific Diarrhea

- Restrict frequency of feedings, whether liquids or solids, in an effort to decrease stimulation of the gastrocolic reflex.
  - In toddlers, 3 meals and a bedtime snack with nothing by mouth in between
- Restrict volume of fluids ingested when excessive.
- Avoid excessive intake of juices.
- Reassure parents of the benign nature of this entity.

Box 1. Fluid and Electrolyte Management of Acute Diarrhea

A. General rules for management of acute diarrhea
   1. Oral rehydration therapy with oral rehydration solution (ORS) containing glucose-electrolytes is the preferred treatment of fluid and electrolyte loss, except as noted herein. These solutions generally contain 25 g/L glucose (or ≥30 g/L rice starch), 45–90 mEq/L sodium, 20–25 mEq/L potassium, and 30 mEq/L bicarbonate. The higher sodium concentration is appropriate for rehydration; the lower concentration is usually adequate for rehydration with mild diarrhea and is appropriate for maintenance.
   2. Moderate to high stool output should be replaced with ORS at 10 mL/kg per stool, if losses cannot be estimated. Losses from emesis should be replaced with ORS at 2 mL/kg per episode of emesis, or as part of replacement for estimated losses.
   3. The use of ORS is labor intensive. If a caregiver is not available to give small amounts of fluid frequently, intravenous (IV) therapy may be necessary. If the child is not severely dehydrated, oral rehydration may be completed at home with close follow-up. Otherwise, IV fluids should include replacement of deficit, ongoing losses, and maintenance fluids. Addition of IV potassium should wait until urine output is established.
   4. ORS therapy is effective for hypernatremic dehydration, as well as for hyponatremic and isotonic dehydration.
   5. Age-appropriate feedings should be continued during acute diarrhea, except as noted herein. Formula should be offered full strength. Diet may be better tolerated if fatty foods and foods high in simple sugars (eg, undiluted juices, soft drinks) are avoided.
   6. Breastfeeding should be continued when possible.
   7. A lactose-free diet is generally unnecessary. If stools worsen on reintroduction of lactose (human milk, cow's milk, or lactose-containing formula), lactose intolerance should be considered. If stools become acidic and contain reducing substances, lactose intolerance is likely.

B. No dehydration
   1. Continue age-appropriate feeding (see A.5 and A.6).
   2. Use ORS only to replace excessive stool output (see A.2).

C. Mild to moderate dehydration (3%–9% of body weight)
   1. Correct dehydration with 50–100 mL/kg ORS over 3–4 hours, and replace continuing losses from stool and emesis with additional ORS (see Special considerations section for special considerations for vomiting.)
   2. Reevaluate hydration and replacement of losses at least every 1–2 hours. This process may require medical supervision (emergency department, hospital outpatient unit, or physician's office).
   3. Once dehydration is corrected, begin feeding (see A.5 and A.6) and continue to correct losses as specified herein.

D. Severe dehydration (≥10% of body weight)
   1. Resuscitate with IV or intraosseous physiologic (normal) saline solution or lactated Ringer injection 20 mL/kg of body weight over 1 hour. Monitor vital signs closely. Repeat until pulse and state of consciousness return to normal. Larger volumes and shorter periods of administration may be required. Delay giving IV potassium until urine output is established.
   2. Determine serum electrolyte levels.
   3. Lack of response to initial resuscitation suggests an underlying problem, such as septic shock, toxic shock syndrome, myocarditis, myocardiopathy, or pericarditis. Persistently poor urine output may be a sign of hemolytic uremic syndrome.
   4. ORS may be initiated when the child's condition has stabilized and mental status is satisfactory. An IV line should be maintained until no longer needed. (See Special considerations section for special considerations for vomiting.)
   5. Feeding may be restarted when rehydration is complete (see A.1 and A.2).

Box 1 (*continued*)

E. Special considerations
   1. Vomiting
      a. Vomiting occurs commonly during acute gastroenteritis.
      b. Children who are dehydrated and vomit usually tolerate ORS.
      c. Intractable severe vomiting, unconsciousness, and ileus are contraindications to ORS treatment.
      d. ORS should be started at 5 mL every 1–2 minutes.
      e. Vomiting usually decreases as dehydration improves; larger amounts can be given at less frequent intervals.
      f. A nasogastric tube can be used for continuous ORS infusion for persistent vomiting or feeding refusal secondary to mouth ulcers (do not use in a comatose child or one who has ileus or intestinal obstruction).
      g. IV fluids should be used if ORS treatment is unsuccessful.
   2. Refusal to take ORS
      a. Children who are not dehydrated may not take ORS because of the salty taste. However, dehydrated children generally take it well.
      a. Giving ORS in small amounts at first allows child to become accustomed to the taste.
      a. ORS can be frozen in ice-pop form.

Modified from American Academy of Pediatrics Provisional Committee on Quality Improvement, Subcommittee on Acute Gastroenteritis. Practice parameter: the management of acute gastroenteritis in young children. *Pediatrics.* 1996;97(3):424–435; and King CK, Glass R, Bresee JS, Duggan C; Centers for Disease Control and Prevention. Managing acute gastroenteritis among children: oral rehydration, maintenance, and nutritional therapy. *MMWR Recomm Rep.* 2003;52(RR-16):1–16.

- High-fat diet may be helpful in some children.
  - Probably is of less importance
- Cholestyramine (2 g by mouth 1–3 times daily) is also effective at times.
  - Duration of use should be restricted because of potential for interference with fat-soluble vitamin absorption.
- This condition is self-limited and typically resolves by 3½ years of age.
  - The only danger is that well-intentioned parents may restrict oral intake to clear liquids repeatedly in an effort to treat the child; this action may result in poor weight gain.
- Bile acid malabsorption is an occasional sequela of gastroenteritis that can produce persistent, watery diarrhea.
  - Will respond to cholestyramine therapy

Protracted Diarrhea of Infancy

- Nutritional rehabilitation should begin at once.
  - The best choices are enteral alimentation with an elemental or modular formula or TPN, peripheral or central.
    - Elemental formulas are composed of predigested components in fixed proportions.
    - Modular formulas allow the clinician to vary the components.
    - In many instances, enteral nutrition is tolerated best by the continuous drip method, and recovery may be more rapid when enteral alimentation is used.
      - Nevertheless, unsuccessful attempts at enteral feeding necessitate initiation of TPN in some infants.
    - Initial treatment with TPN and a gradually increasing, continuous enteral drip is a good approach to patients who do not tolerate an elemental diet alone.
    - Stool output and weight gain may be measured to assess the infant's response.
  - During treatment, further workup, as indicated
    - Upper GI series with small-bowel radiography
    - Barium enema
    - Small-bowel biopsy
      - If disaccharidase levels are abnormal on small-bowel biopsy, disaccharides should be avoided.
    - Proctoscopy

Malabsorption Syndromes

- Oral enzyme supplements are available for lactase and sucrase deficiency.
- Congenital deficiency of enterokinase is reversed with very small amounts of pancreatic replacement.

Intestinal Lymphangiectasia

- Treatment includes the dietary use of medium-chain triglycerides and avoidance of long-chain fat.
- Protection from and early treatment of infection also are important.

Autoimmune Enteropathy

- Immunosuppressive therapy

Irritable Bowel Syndrome

- Increased fiber in the diet
- Anticholinergics
- Tricyclic antidepressants for diarrhea-predominant irritable bowel syndrome, under experienced supervision

WHEN TO REFER

- Persistent diarrhea when the workup results for routine infectious causes is negative
- Steatorrhea
- Diarrhea or steatorrhea (or both) causing weight loss or failure to thrive
- Diarrhea associated with fever, chronic anemia, or abdominal pain without an obvious explanation
- When IBD is a consideration

WHEN TO ADMIT

- Acute or chronic diarrhea with mild to moderate dehydration that cannot be managed successfully with outpatient rehydration solution
- Dehydration >10% of body weight
- Diarrhea with intractable vomiting
- Severe electrolyte imbalance, including hypernatremic dehydration or serum potassium level <3.0 mEq/L
- Laboratory evidence suggesting HUS
- Chronic diarrhea or steatorrhea (or both) with persistent signs of malnutrition that is unresolved with outpatient management
- Severe manifestations of IBD unresponsive to routine outpatient treatment

FOLLOW-UP

- Patients undergoing rehydration therapy should be monitored frequently and need close follow-up.

COMPLICATIONS

- Chronic diarrhea can lead to failure to thrive.

PREVENTION

- Acute gastroenteritis caused by rotavirus can be prevented by oral rotavirus vaccine during infancy.

DEFINITION

- Patients with ambiguous genitalia have *disorders of sex development* (DSD).
  - Previously termed *intersex conditions*
- The nomenclature used to describe atypical sexual differentiation has changed.
  - Concerns were that the terminology was pejorative to patients and confusing to medical practitioners.
- Historically, the term *male pseudohermaphrodite* was used to describe the patient with incompletely masculinized external genitalia possessing XY chromosomes and a typical number of autosomes (also known as *46,XY karyotype*).
  - These conditions, as well as conditions in which the testes do not develop normally, are now denoted as *46,XY DSD*.
- The term *female pseudohermaphrodite* was used to describe the patient with 46,XX karyotype and with masculinized external genitalia.
  - Currently, these disorders, as well as disorders of ovarian development, are denoted as *46,XX DSD*.
- Sex chromosome DSD.
  - Now describes sex chromosome abnormalities that affect gonadal development.
  - These conditions may or may not involve genital ambiguity.
- In rare cases, a patient may have ovarian and testicular tissue.
  - These patients had been called *true hermaphrodites* in the past.
  - They are now considered to have *ovotesticular DSD*.

SIGNS AND SYMPTOMS

History

- Evaluation of a neonate with a disorder of sexual differentiation must include a detailed obstetric and family history.
- The patient's mother should be asked about medication use and symptoms of virilization during pregnancy.
  - May occur in aromatase deficiency or with androgen-secreting maternal ovarian or adrenal tumors
- Family history should elicit history of
  - Genital abnormalities
  - Consanguinity
  - Unexplained neonatal deaths, especially in apparently phenotypic males (because males with congenital adrenal hyperplasia [CAH] will not have the clue of genital ambiguity to raise suspicion for the possibility of adrenal crisis)
  - Infertility
  - Disorders of puberty
- Many conditions associated with ambiguous genitalia are sporadic or inherited in an autosomal-recessive manner.

Physical Examination

- Initial physical examination should begin with an assessment of the general health of the patient and an evaluation for malformations or dysmorphic features.
- Physical findings in patients with DSD may range from an apparently normal phenotype to complete ambiguity.
- Unstable vital signs or hypoglycemia with no apparent cause should raise concern about cortisol deficiency associated with CAH.
- Typically, shock in patients with CAH does not develop until day 4 to 5 of life.
- Patients with ambiguous genitalia may benefit from earlier diagnosis of salt loss and signs of cortisol deficiency than phenotypically normal patients.
- Midline abnormalities, such as cleft palate, may be associated with hypopituitarism and low gonadotropin levels, leading to microphallus.
- Increased skin pigmentation caused by elevated levels of adrenocorticotropic hormone (ACTH) occurs well after the newborn period and, thus, is not helpful in early diagnosis.
- Stretched penile length in a term male neonate should be >2 cm.
  - Average length is ~3.5 cm.
- A normally formed phallus and scrotum indicate that testosterone production in the critical window of male differentiation was appropriate.
- Micropenis (penile length <2 cm) often indicates gonadotropin deficiency and may be a sign of hypopituitarism.
- Position of the urethral meatus should be noted.
  - Sometimes requires observation of urination.
  - A urogenital sinus can be mistaken for the urethra.
  - Indentation at the end of the glans penis can be mistaken for the penile urethra.

- The labioscrotal folds should be examined for
  - Degree of fusion
  - Symmetry
  - Rugosity
  - Color
- Presence or absence of a vaginal opening should be established.
- Gonads, when palpable bilaterally, are most often testes but might be ovaries or ovotestes as well.
- A unilaterally palpable and symmetric gonad may be a testis.
- Sweeping the fingers down the path of the inguinal canal may allow palpation of gonads that could not otherwise be located.
- If gonads are palpable, the neonate is not a virilized female with CAH because these patients have nonpalpable gonads (ovaries) that are situated in the pelvis.
- Nongenital anomalies on physical examination should also be noted and documented.
- Genital anomalies may occur in conjunction with an overall pattern of malformation or may be seen in certain syndromic diagnoses.
- Dysmorphic features or specific nongenital anomalies may raise suspicion for one of these conditions.
- Discordance between the phenotypic sex and genetic sex (known ahead of time as a result of prenatal testing) should raise suspicion for the possibility of DSD.

DIFFERENTIAL DIAGNOSIS

- Differential diagnosis of the neonate born with developmental anomalies of the external genitalia is extensive, given the complicated process of human sexual differentiation.
- **Table 1** lists differential diagnosis of adrenal enzyme defects.

46,XX DSD

- Late-onset, or non-classic, 21-hydroxylase deficiency begins with excessive or premature acne and sexual hair.
  - Milder, non–life-threatening form of CAH that does not cause genital ambiguity
  - May be associated with increased growth and bone age advancement
- 17-Hydroxylase deficiency.
  - Females are phenotypically normal at birth but will not progress through pubertal changes.
  - Primary amenorrhea may be the presenting feature.
- 3β-Hydroxysteroid dehydrogenase deficiency.
  - Genetic females may be phenotypically normal or have varying levels of clitoromegaly or labial fusion.
  - Varying degrees of salt loss, as a result of aldosterone deficiency.
- Aromatase deficiency.
  - Females may exhibit mild virilization in addition to osteopenia and delayed bone age (given the estrogen deficiency).
  - Genetic male fetuses may have genital ambiguity as well.

46,XY DSD

- 3β-Hydroxysteroid dehydrogenase deficiency
  - Affected males may be incompletely masculinized at birth.
  - Often experience salt loss or adrenal crisis in infancy.
  - May experience gynecomastia around the time of puberty.
  - Elevated levels of enzyme substrates, such as dehydroepiandrosterone and pregnenolone.
- Aromatase deficiency
  - Males with aromatase deficiency will be tall and have delayed bone age and osteoporosis caused by estrogen deficiency.

Defects in Androgen Action

- Development of female secondary sexual characteristics.
  - Pubic and axillary hair is sparse, if present at all.
  - Menarche cannot occur.
- Incomplete forms of androgen resistance have great phenotypic variability.
  - External genitalia may range in appearance from completely ambiguous to mildly hypoplastic male genitalia with a small but normally formed phallus.
  - Hypoplastic wolffian duct structures are typically present.
  - Müllerian derivatives are absent because of production of antimüllerian hormone (AMH).
  - At puberty, virilization is usually incomplete.
  - Gynecomastia often becomes apparent.
  - Axillary and pubic hair is normal in amount and distribution.
- External genitalia are phenotypically female, given the inability of the tissue to respond to dihydrotestosterone (DHT).

Table 1. Differential Diagnosis of Adrenal Enzyme Effects

	Newborn	Postnatal	Salt losing=+
Deficiency	**Phenotype**	**Virilization**	**Hypertension=***
StAR (also known as lipoid congenital adrenal hyperplasia)	Infantile female	–	+
3β-Hydroxylase (3βHSD)	Ambiguous in XY Female or ambiguous in XX	+ +	+ +
17α-Hydroxylase ($P450_{c17}$)	Infantile female	–	*
11β-Hydroxylase ($P450_{c11}β$)	Male in XY Ambiguous in XX	+ +	* *
21-Hydroxylase ($P450_{c21}$)	Male in XY Ambiguous in XX	+ +	+(50%) +(50%)
18-Hydroxylase ($P450_{c11AS}$)	Normal	–	+

Abbreviations: StAR, steroidogenic acute regulatory protein function; +, positive; –, negative.

From Styne DM. *Pediatric Endocrinology: A Clinical Handbook*. Cham, Switzerland: Springer International Publishing; 2016. With permission of Springer.

- Müllerian structures, such as the cervix and uterus, are absent or hypoplastic.
  - Production of AMH by the fetal Sertoli cells is normal.
  - The vagina ends in a blind pouch.

5α-Reductase-2 Deficiency

- Secondary sexual characteristics, such as increased muscle mass and voice deepening

Disorders of Gonadal Differentiation (Sex Chromosome DSD)

- Klinefelter syndrome
  - Before puberty, patients have
    - Decreased upper segment to lower segment ratios.
    - Small testes.
    - Increased incidence of developmental delay (mainly in the areas of speech and language).
    - Behavioral problems.
    - Males are taller than expected from age 5–6 years onward.
  - Puberty is not usually delayed because Leydig cell function is characteristically less affected than seminiferous tubule function.
  - Testosterone is often adequate to stimulate pubertal development.
  - Serum gonadotropin levels increase after the onset of puberty, as the testes become firm and rarely grow >3.5 cm in diameter.
  - After the onset of puberty, histologic changes of seminiferous tubule hyalinization and fibrosis, adenomatous changes of the Leydig cells, and impaired spermatogenesis occur.
  - Gynecomastia is common.
  - Variable degrees of male secondary sexual development.
- Turner syndrome (syndrome of gonadal dysgenesis)
  - Turner syndrome (45,X karyotype) is associated with
    - Lack of secondary sexual development at time of puberty.
    - Short stature.
    - Characteristic female phenotype often includes webbing of the neck.
  - Patients have streak gonads consisting of fibrous tissue without germ cells.
  - Pubic hair may appear late and is usually sparse.
    - Adrenarche progresses even in the absence of gonadarche.

- Serum gonadotropin concentrations are extremely high between birth and age 4 years.
  - Decrease toward the normal range in prepubertal patients and then increase again dramatically after age 10 years.
- Because of decreased ovarian secretion of estrogens, puberty does not usually begin spontaneously.
  - Patients have no pubertal growth spurt and reach a mean final height of 143 cm.
  - Growth hormone function is usually typical.
- Various mosaic forms have been identified, with such karyotypes as 45,X/46,XX or 45,X/46,XY.
- These patients may have any phenotype varying from normal female to normal male to manifestations of many of the features of Turner syndrome.
  - Some have apparently normal gonadal function.
  - Others have abnormality of one X chromosome, such as a ring X, which may be associated with intellectual disability and a variety of congenital malformations.

- Other disorders of gonadal development include
  - In complete gonadal dysgenesis, 46,XY karyotype individuals fail to develop normal testes.
  - Instead, they have
    - Gonadal streaks
    - Müllerian duct development
    - Wolffian duct regression
    - Female external genitalia
  - Usually associated with ambiguous genitalia and partial development of the wolffian and müllerian ducts.
  - In gonadal regression or vanishing testes syndrome, the testes are lost after the external genitalia and internal structures have formed.
  - These 46,XY individuals will be phenotypically male except for absence of both testes.
  - Patients may phenotypically resemble those with Klinefelter syndrome.
- Ovotesticular DSD
  - Patients with ovotesticular DSD have ovarian and testicular tissue present.
  - Most patients have a 46,XX phenotype, and the remainder have a 46,XY karyotype or 46,XX/46,XY chimerism.
  - Great phenotypic variability exists in the internal and external genitalia in these patients.

DIAGNOSTIC APPROACH

- In males, even very mild hypospadias can be considered to represent incomplete masculinization.
  - Most uncomplicated cases do not need diagnostic evaluation.
  - More severe degrees of hypospadias, especially when a testis is not palpable, should raise concern about an identifiable abnormality.
  - In an apparently phenotypic female, mild clitoromegaly may represent
    - Severe under-virilization in a genetic male who has undescended testes
    - Masculinization of a female fetus
- Specific recommendations for which genital findings should elicit concern for a sexual development disorder.
  - An apparent male born at term with the following characteristics:
    - Bilateral nonpalpable testes
    - Micropenis
    - Perineal hypospadia
    - Single undescended testis with hypospadia of any degree
  - An apparent female with the following characteristics:
    - Clitoral hypertrophy of any degree
    - Posterior labial fusion (but not just labial adhesions)
    - Inguinal or labial mass
  - All neonates with truly ambiguous genitalia and thus indeterminate gender.
  - Neonates with family history of DSD or discordance between apparent gender and a previously obtained prenatal karyotype.
  - Because the testes do not normally descend until ~34 weeks of gestation, significantly preterm males with nonpalpable testes alone do not necessarily require evaluation.
- Newborn screening should eliminate cortisol and aldosterone deficiency in diagnostic time.
- Diagnosis of P450c11 hydroxylase deficiency is usually made after the discovery of elevated levels of 11-deoxycortisol (compound S).
- Diagnosis of aromatase deficiency is made around the time of puberty.
- Defects in androgen action are suggested by elevated levels of testosterone.
- 5α-Reductase-2 deficiency.
  - Ovotesticular DSD
    - Ovotesticular DSD should be considered in all patients with DSD.

- A 46,XX/46,XY karyotype or a bilobate gonad in the inguinal region or labioscrotal folds should raise suspicion.

LABORATORY FINDINGS

- Basic serum chemistries should be obtained immediately to evaluate for salt wasting or hyperkalemia associated with CAH.
  - Abnormalities may take days to become apparent.
- Normal electrolyte values in the few days after birth do not exclude salt loss.
- Karyotype will establish whether the patient is genotypically XX or XY (or other) and should always be performed.
  - Results from an urgently ordered karyotype can be available within ~3 days in some cytogenetics laboratories.
- Endocrine testing generally consists of measurement of
  - 17-Hydroxyprogesterone (17-OHP)
  - Testosterone
  - DHT
  - Androstenedione
  - Follicle-stimulating hormone
  - Luteinizing hormone
  - AMH
- Tests should be performed in a national specialty laboratory with pediatric standards rather than the local laboratory.
  - Most local laboratories are unlikely to have pediatric standards or appropriately sensitive techniques.
  - On the basis of these results, additional tests may be performed.
- In the first weeks after birth, measurement of testosterone may reveal the amplitude of the episodic spike of testosterone.
- After this period, human chorionic gonadotropin (hCG) administration will help determine whether functional Leydig cells are present (given that functional cells will secrete testosterone in response to the hCG).
- Serum testing of the steroid hormones involved in the pathways for cortisol and testosterone is indicated in many cases because the rare forms of CAH will not uniformly cause elevations in 17-OHP levels.
- In some cases, stimulatory testing with ACTH is necessary.
- Newborn screening for 21-hydroxylase deficiency (but not other forms of CAH) is now done in all 50 US states, the District of Columbia, and Guam.
  - Results can be returned several days after the specimens are drawn.
  - Available within the first week of life but not always before clinical symptoms develop.
  - This screening test is most helpful in diagnosing the normal-seeming but affected male.
  - A trial of testosterone injections (eg, 25 mg of testosterone enanthate intramuscularly every month for 3 months) is given in some equivocal cases to assess whether phallus size responds to androgen, which may eliminate androgen resistance as a diagnostic possibility.
    - The effect of this cannot be assessed for several months.
- 5α-Reductase-2 deficiency.
  - Laboratory testing reveals abnormally high testosterone to DHT ratios with normal to elevated testosterone and low to undetectable DHT.
- Confirmatory testing via mutation analysis of the 5α-reductase-2 gene can be performed but is not yet available commercially.

IMAGING

- Imaging is useful to determine internal anatomy.
- Ultrasonography.
  - Determination of the presence and appearance of müllerian structures
    - Lack of müllerian structures implies that AMH was produced from testicular tissue and that the underlying problem is an abnormality of testosterone or DHT synthesis or action.
  - Renal problems (eg, in Frasier syndrome)
  - Visualization of the adrenal glands
  - Visualization of the gonads
    - Magnetic resonance imaging may be required, particularly if the gonads are intra-abdominal.
  - Defects in androgen action
    - Shown by absence of the corpus and cervix and the presence of testes

TREATMENT APPROACH

- A team to address the multiple issues surrounding management of patients with DSD may include
  - Endocrinologist
  - Pediatric surgeon
  - Pediatric urologist
  - Neonatologist
  - Geneticist
  - Ethics specialist
  - Psychologist or psychiatrist
  - Social worker
- Gender assignment should be avoided after delivery and during evaluation.
  - The neonate should be referred to using gender-neutral terms such as *your baby* or *the baby* rather than *he* or *she*.
- Completion of the birth certificate should be delayed.
- The family should be supported by an experienced and well-trained social worker and psychologist.
- The ultimate gender assignment is based on
  - Underlying diagnosis
  - Genital appearance
  - Surgical options
  - Potential for fertility and sexual function
  - Family's personal and cultural beliefs
- When a gender assignment is reached, the gender role should be supported, although parents should understand that not all patients with a given diagnosis will identify themselves in the same way over time.
- Surgical reconstruction is increasingly deferred until the patient is able to participate in the decision-making process.
- Gender identity is the personal conception of oneself as male or female.
  - It is distinct from sexual orientation and gender role.
  - Influences on gender identity include
    - Hormonal effects (specifically androgen effect on the prenatal brain)
    - Brain structural differences
    - Assigned sex and rearing
    - Sex-steroid effects at the time of puberty
  - Given this complexity, definitive predeterminations of gender identity are unlikely to be fully accurate.
  - Some patients are later dissatisfied with assigned gender.
- Outcome data for gender identity in DSD are relatively sparse; the largest study to date showed
  - Genetic males with active prenatal androgen effects should be raised as males.
  - Female neonates virilized as a result of CAH should be raised female.
- Gender identity outcomes are more difficult to predict in other disorders, with high rates of gender change and gender dysphoria occurring with some diagnoses.
- This variability in gender identity again speaks to the reasoning behind deferring genital surgery in infancy.
- In some cases, early surgery is indicated for medical reasons (eg, long common urogenital channel).
- Potential for malignant degeneration of a gonad in certain DSD involving Y chromosome material must be considered.
- Prophylactic gonadectomy was previously performed early in all cases of 46,XY DSD; now, tumor risk is predicted based on molecular diagnosis.
- Guidelines for timing of gonadectomy have been proposed, but consensus is needed.
- Long-term psychologic support is required for most patients with DSD.
  - Help should be provided by a mental health professional, preferably one experienced in DSD.
  - National and local support groups are available for families.
  - Historically, there has been stigma associated with DSD, and care should be taken to reassure the family that there is nothing shameful about the DSD diagnosis.
  - The underlying condition and management (including surgical decisions) should be discussed with the child over time in an age-appropriate manner.

SPECIFIC TREATMENTS

Equivocal Cases

- A trial of testosterone injections (eg, 25 mg of testosterone enanthate intramuscularly every month for 3 months) is given in some equivocal cases to assess whether phallus size responds to androgen, eliminating substantial androgen resistance.
  - The effect of this cannot be assessed for several months.

Defects in Androgen Action

- Removal of testicular tissue is indicated, given the increased risk for neoplasm after puberty.
  - The timing of removal is controversial.
  - After removal of the testes, estrogen replacement is provided.

5α-Reductase-2 Deficiency

- Given the phenotypic appearance at birth, many affected male children with 5α-reductase deficiency are raised as female.
- Following physical changes that occur around the time of puberty, some patients may adopt a male gender role in adolescence or early adulthood.

Disorders of Gonadal Differentiation (Sex Chromosome DSD)

- Turner syndrome (syndrome of gonadal dysgenesis)
  - Growth hormone treatment increases growth rate and adult stature.
  - Estrogen treatment is initiated in adolescence to allow feminization.

WHEN TO ADMIT

- Patients with significant electrolyte abnormalities, such as hyponatremia and hyperkalemia
- Patients with dehydration
- Patients with hypoglycemia

WHEN TO REFER

- All patients with ambiguity of the external genitalia should be evaluated immediately by an experienced multidisciplinary team that includes a pediatric endocrinologist.
  - Necessitates transfer to a medical center with a neonatal intensive care unit and appropriate pediatric subspecialists
  - The patient should never be sent home and referred to subspecialty care as an outpatient.
- Indications for referral include
  - A male-seeming neonate with
    - Bilateral nonpalpable testes
    - Micropenis
    - Perineal hypospadias
    - Single undescended testes with hypospadias of any degree
  - A female-seeming neonate with
    - Clitoral hypertrophy of any degree
    - Posterior labial fusion (not adhesion)
    - Inguinal or labial mass
  - Patient with family history of DSD
  - Patient with discordance between genital appearance and prenatal karyotype

COMPLICATIONS

- DSD is considered an endocrine emergency.
  - Many common forms of DSD (ie, CAH) are associated with
    - Life-threatening electrolyte abnormalities
    - Hypotension
    - Shock
- The psychologic stress to the family cannot be overstated.
- In its most serious form, cortisol and aldosterone deficiency are severe enough to result in
  - Severe hyponatremia
  - Hyperkalemia
  - Dehydration
  - Hypotension
  - Shock
  - Death
- Male neonates die more frequently than female neonates.
  - As a result of their visibly normal phenotype at birth, the condition is not suspected.
- Female neonates with virilization are usually evaluated quickly.
- Disorders of gonadal differentiation (sex chromosome DSD).
  - In Klinefelter syndrome, the risk of breast cancer is increased.

Dizziness and Vertigo

DEFINITION

- Dizziness and vertigo are very different symptoms with different clinical implications.
- Dizziness.
  - Term commonly used by patients to describe subjective symptoms such as faintness, giddiness, light-headedness, or unsteadiness.
  - Patients with simple dizziness do not describe the room spinning around them and do not have nystagmus.
- Vertigo.
  - Sensation of rotation, spinning, or whirling motion.
  - True vertigo is accompanied by nystagmus.

HISTORY

- History should ascertain
  - Description of events.
  - Onset/precipitating event (eg, trauma, standing up, change in head position, excessive strain/exertion such as flying, diving, coughing, sneezing).
  - Characterization in patient's words (eg, "room spinning").
  - Context (eg, vision changes, hearing changes, medicine or toxin exposure).
  - Associated events.
    - Aura
    - Scintillating scotomas
    - Oral paresthesias
    - Tinnitus
    - Drop attacks
    - Seizures
    - Loss of consciousness
    - Altered mental status
  - Observations from others, including
    - Eye deviations
    - Nystagmus
    - Unsteady gait or evidence of dysequilibrium
    - Loss of consciousness
  - When young children cannot describe dizziness or vertigo, observers tend to apply these terms to a child who is unsteady while standing.
- Medical history/review of systems
  - Hearing loss, recent illnesses, history of trauma or blood loss.
  - Medication history.
  - Cardiac symptoms, including
    - Palpitations
    - Chest pain
  - Neurologic symptoms, including
    - Headache
    - Motion sickness
  - Family history, including
    - Neurofibromatosis
    - Seizures
    - Migraines
    - Syncope
    - Sudden death
  - In adolescents, as indicated, consider a full HEADSSS assessment.
    - **H**ome
    - **E**ducation
    - **A**ctivities
    - **D**rugs
    - **S**exuality
    - **S**uicide/Depression
    - **S**afety
  - Alternatively, at a minimum
    - Home situation
    - Educational status
    - Sexual history and last menstrual period
    - Stressors

PHYSICAL EXAMINATION

- Vital signs.
  - Temperature.
  - Heart rate.
  - Blood pressure.
  - Orthostatic vital signs.
  - It may be useful to compare weight with previous weights when assessing hydration status.
- Mental status.
- Volume status.
- Assess for anemia (eg, pale conjunctiva).
- Examine head and neck and pay particular attention to ears.
  - Vesicles may suggest herpes zoster (Ramsay Hunt syndrome).
  - A distorted tympanic membrane may be seen with otitis media, cholesteatoma, and perilymph fistula.
  - Two useful maneuvers that may help in the diagnosis of perilymph fistula are
    - Application of pressure to the tragus to occlude the external auditory canal.
    - Pneumatic otoscopy.
    - Both may induce nystagmus or vertigo and transiently worsen hearing loss.
- Complete examination of the cardiac and neurologic systems.

- The Dix-Hallpike maneuver (Nylen-Barany test) can help localize the source of nystagmus or vertigo.
  - To provoke an episode, move the child rapidly from a sitting to supine position with the head 45° below the edge of the table and turned 45° to one side.
  - The ear that is facing the floor when the nystagmus is elicited is the affected side.
    - Nystagmus that resolves when the child fixates on an object is suggestive of peripheral or vestibular disease; persistent nystagmus suggests a central nervous system (CNS) disorder.

DIFFERENTIAL DIAGNOSIS

- Most episodes of dizziness and vertigo can be diagnosed by history and physical examination alone.
- See **Table 1** for suggested diagnoses based on history.

Dizziness

- Middle ear disease
  - Middle ear effusion may cause deterioration in vestibular balance and motor function.
  - If not self-limited, symptoms usually resolve after placement of tympanostomy tubes.
- Pre-syncope and syncope related to
  - Fever
  - Dehydration
  - Orthostatic hypotension
  - Vasovagal episodes
  - Cardiac arrhythmias
- Anemia
  - From acute or chronic blood loss
  - From a congenital condition such as sickle cell disease
- Cardiovascular
  - Any heart disease or arrhythmia that affects cardiac output
  - Hypertension
- Hypoglycemia
- Endocrine cause
  - Hyperthyroidism
  - Hypothyroidism
  - Addison disease
- Ocular disorders
  - Refractive errors
  - Astigmatism
  - Amblyopia
  - Strabismus
- Acute cerebellar problems, especially in young children
  - Postviral acute cerebellar ataxia
  - Posterior fossa tumors
- Multiple sclerosis
  - In adolescents, particularly girls, ataxia may be described as dizziness.
- Medications such as
  - Aminoglycosides
  - Phenytoin
  - Loop diuretics
  - Nonsteroidal anti-inflammatory drugs
- Pregnancy
- Anxiety or panic attacks

Vertigo

- The causes of vertigo can be differentiated based on 3 elements of the history.
  - Whether the vertigo is acute or chronic
  - Whether episodes are recurrent
  - Whether the vertigo is accompanied by hearing loss
- Acute episodic or recurrent vertigo.
  - Usually not accompanied by hearing loss.
  - Migraine headaches and related syndromes.
    - Benign paroxysmal torticollis of infancy is thought to be a migraine variant.
      - Episodes of recurrent head tilt for hours or days, often associated with vomiting, agitation, pallor, and ataxia
    - Benign paroxysmal vertigo of childhood also is considered a migraine variant.
      - Sudden onset of extreme unsteadiness and inability to stand, usually with nystagmus and sometimes with vomiting.
      - Episodes last seconds to minutes.
      - Family history of migraines; many develop typical migraines later in life.
    - Basilar artery migraines.
      - Scintillating scotomas or visual obscuration, oral paresthesias, tinnitus
      - Occasionally *drop attacks* with or without loss of consciousness
      - Often followed by a pounding headache
  - Seizures that are associated with vertigo are followed by an alteration in or loss of consciousness.
  - Perilymph fistula.
    - Abnormal connection between inner and middle ear spaces, which may be congenital or acquired by trauma

Table 1. Differential Diagnoses of Dizziness and Vertigo

Information	Possible Diagnoses
Family History	
Neurofibromatosis	Acoustic neuroma
Seizure disorder	Seizure
Migraines	Benign paroxysmal torticollis of infancy
	Benign paroxysmal vertigo of childhood
	Migraine
Unexplained syncope or sudden cardiac death	Dysrhythmias
Anxiety, panic disorders	Anxiety
Medication History	
Aminoglycosides, loop diuretics, phenytoin, nonsteroidal anti-inflammatory drugs, chemotherapeutic agents, quinine	Ototoxicity
	Intoxication
Medical History	
Acute or chronic blood loss	Anemia
Palpitation or chest pain	Dysrhythmias
	Anxiety, panic disorder
Recent life stressor	Anxiety
Last menstrual period	Pregnancy
Motion sickness	Benign paroxysmal vertigo of childhood
	Migraine
Recent upper respiratory infection	Vestibular neuritis
Fever	Otitis media
	Labyrinthitis
Ear trauma, barotrauma	Perilymph fistula
Headache	Migraine
	CNS disease
Head trauma	Temporal bone fracture
	Labyrinth or brain stem concussion
	Cerebellar contusion
	Perilymph fistula
Neurologic deficits	CNS tumor
	Multiple sclerosis

Table 1 (*continued*)

Information	Possible Diagnoses
Hearing loss	Cholesteatoma
	Acoustic neuroma
	Temporal bone fracture
	Perilymph fistula
	Labyrinth concussion
	Labyrinthitis
	Ramsay Hunt syndrome
	Meniere disease
Triggered by change in head position	Benign paroxysmal positional vertigo
	Perilymph fistula
	Vestibular neuritis
	Acute labyrinthitis
Loss of consciousness or altered mental status	Seizure
	Dysrhythmias
	Vasovagal syncope
	CNS disease
	Hypoglycemia

Abbreviation: CNS, central nervous system.

- Benign paroxysmal positional vertigo.
  - Acute episodes of severe vertigo precipitated by a change in head position
  - Associated with nystagmus, nausea, and vomiting but not hearing loss
- Acute febrile vertigo.
  - Usually associated with severe otitis media leading to labyrinthitis
    - Patient uncomfortable, with ear pain and severe vertigo
    - Usually with nausea, vomiting, and nystagmus
  - Vestibular neuritis
    - Consider if vertigo preceded by viral illness.
    - Not associated with hearing loss.
- Acute vertigo related to head or ear trauma.
  - May be associated with hearing loss
  - May create perilymph fistula
- Chronic persistent vertigo.
  - Especially if accompanied by neurologic signs
  - Usually is indicative of CNS disease
  - Meniere disease
    - Vertigo
    - Fluctuating hearing loss
    - Pressure in the ear
    - Tinnitus
  - CNS tumors
    - Acoustic neuromas (seen in neurofibromatosis type II)
  - Demyelinating disorders
  - Degenerative disorders

LABORATORY EVALUATION

- Laboratory testing has a limited role in the evaluation of dizziness and vertigo.

- Evaluation is guided by clinical suspicion and may include
  - Blood glucose and chemistries
  - Complete blood cell count
  - Metabolic panel
  - Thyroid function tests
  - Medication levels
  - In girls, pregnancy testing

IMAGING

- Imaging is guided by clinical suspicion.
  - Magnetic resonance imaging of brain or other neuroimaging may be helpful.

DIAGNOSTIC PROCEDURES

- Diagnostic procedures may be obtained as guided by clinical suspicion.
  - Electrocardiogram
    - Consider especially if history suggests syncope or pre-syncope.
  - Electroencephalogram
  - Audiometry and electronystagmography
    - Consider in evaluation of vertigo.

TREATMENT APPROACH

- Treatment is aimed at the underlying disease entity.

SPECIFIC TREATMENT

- Vestibular suppressants may be used to relieve the symptoms of vertigo and nausea.
  - Diazepam
  - Meclizine (for children and adolescents >12 years)
  - Dimenhydrinate
- Orthostatic hypotension with dizziness.
  - Hydrate appropriately with intravenous fluids as needed.
  - Provide reassurance and education.
    - Caution against rising suddenly.
    - Educate about necessity of putting the head lower than the heart when symptoms occur.
- Labyrinthitis.
  - Treat with antibiotics.
- Migrainous vertigo.
  - Treatment is symptomatic and targeted to the treatment of migraines.
- Panic attack or significant stress presenting with dizziness.
  - Further history should be obtained, including any suicidal ideation.
  - Referral for counseling should be considered.
- Postinfectious vestibular neuritis.
  - Treatment is symptomatic and supportive.
  - Evidence suggests that prednisone may be helpful.

WHEN TO REFER

- Acute ataxia
- A clear history of vertigo, especially with other neurologic signs or after head trauma or barotrauma
- Suspected perilymph fistula or cholesteatoma
- Suspected seizure
- Complicated migraine

WHEN TO ADMIT

- Bacterial or suppurative labyrinthitis
- Head trauma with temporal bone fracture
- Space-occupying lesions
- Potentially life-threatening cardiac dysrhythmias
- Labile hypertension

Down Syndrome

DEFINITION

- Down syndrome (DS) is a constellation of abnormalities caused by triplication or translocation of chromosome 21.

SIGNS AND SYMPTOMS

- Most common physical features
  - Hypotonia
  - Relatively small brachycephalic head
  - Epicanthal folds
  - Flat nasal bridge
  - Upward-slanting palpebral fissures
  - Brushfield spots
  - Small mouth
  - Small and often square-shaped ears
  - Increased skin at the nape of the neck
  - Single transverse palmar crease
  - Short fifth finger with clinodactyly
- Intellectual disability
  - Degree can only be determined with time.
  - Although most individuals with DS have milder forms of intellectual disability, some may be more significantly affected.
  - According to the *Diagnostic and Statistical Manual of Mental Disorders*, 5th Edition, health professionals must consider the person's ability or impairment across 3 skill areas.
    - Conceptual
    - Social
    - Practical life skills

LABORATORY FINDINGS

- Chromosomal analysis
  - If analysis was done, review results with the family and add the report to the newborn's medical record.
  - If the results of prenatal chromosome testing are not available, obtain a blood sample for postnatal cytogenetic analysis to confirm diagnosis and rule out a chromosome translocation.
  - If there was no prenatal diagnosis and the newborn is clinically suspected of having DS, obtain blood for a chromosome analysis and request rapid results.
    - Fluorescent in situ hybridization (FISH) analysis results should be available within 24–48 hours.
  - If analysis confirms that an extra chromosome 21 is present, obtain a complete chromosome analysis to determine if a translocation is present.
  - The confirmation of DS diagnosis by chromosome analysis helps parents accept the clinical diagnosis and forms the basis of genetic counseling about the risk of recurrence.
- Thyroid screening
  - Thyroid-stimulating hormone (TSH)
    - Newborn, 6 months, 12 months, and annually thereafter
  - Serum-free thyroxine
- Tissue transglutaminase immunoglobulin A (IgA) level and simultaneous serum IgA
  - Screen for celiac disease.
- Complete blood cell count
  - Newborns
- Hemoglobin
  - Annual screening for all children
- Ferritin and C-reactive protein (CRP)
  - Screen any child at risk of iron deficiency on the basis of decreased iron intake.

IMAGING

- Cervical spine radiography (neutral position)
  - Must be performed for children with
    - Neck or radicular pain
    - Weakness, spasticity, or change in tone
    - Gait difficulties
    - Hyperreflexia
    - Change in bowel or bladder function
- Echocardiography
  - Fetal echocardiography can improve outcome for mother and baby if fetus has been prenatally diagnosed with DS.
  - Because congenital heart defects occur in ~50% of neonates with DS, echocardiography should be done in all neonates and interpreted by a pediatric cardiologist (even if a prenatal echocardiogram has been obtained).

TREATMENT APPROACH

- The first important aspect of helping families with a neonate with suspected DS is to congratulate them on the birth of their baby.
- Ideally, both parents, or the mother and a significant other, are present and delivery of news about the neonate with the suspected diagnosis is coordinated by the obstetrician and pediatrician.
- Diagnosis should be given as soon as possible after the mother has recovered from immediate delivery, in a private setting, by physicians familiar with the patient.

- As soon as diagnostic FISH and karyotype results are available, share results with parents and review clinical manifestations of DS.
- Refer parents for genetic counseling if they were not seen prenatally by a genetic counselor.
- Present the expectations for a child with DS to families and enable them to learn the realities and possibilities for their child's healthy and productive life.
- Share with families how, when, and what to tell siblings, family, and friends.
- Assure them that resources and guidance for care of a child with long-term disabilities are available.
- Encourage them to enjoy their newborn.
- Discuss the efficacy and availability of early intervention resources.
- Arrange for follow-up with families to give them time to begin to adjust to the information and formulate questions.
- Offer to meet extended family members to answer questions.
- Because newborn hospital care is often provided by a physician who is not part of the newborn's medical home, ensure appropriate communication for smooth transition.
- Adoption.
  - Most families are able to meet the needs of their child born with DS.
  - Some have greater initial difficulty and require more extended counseling.
  - In rare cases, a family will not be able to accept a child who has DS.
    - In this event, adoption should be discussed.
  - In many instances, families are waiting to adopt children who have DS, and families with one child with DS may wish to adopt another.
  - Contact the National Down Syndrome Adoption Network for information (www.ndsan.org).

SPECIFIC TREATMENTS

Birth–1 Month of Age

- When the clinical diagnosis of DS is considered
  - Order rapid chromosome testing.
  - Counsel the family about the suspected diagnosis.
  - Carefully assess the neonate (see Complications section).
- Complementary and alternative or integrative therapies
  - Discuss treatments that are considered integrative.
  - Facilitate parents' understanding of which therapies are recognized as safe and which are potentially dangerous.
  - Many families have questions about cognitive and developmental improvement with supplemental vitamins or high-dose vitamins and minerals.
  - No studies have validated improvement, and there are known side effects of high doses of some vitamins.
  - Ensure that parents understand the risks and that excessive doses are avoided.

1 Month–1 Year of Age

- Parents' anxiety and questions decrease with time.
- For the initial months, they need to be able to depend on the availability of their medical home.
- Using a system of care for the infant with special health care needs is important.
- Consultation with a dietitian, nurse practitioner, or social worker can supplement family care.
- Questions.
  - Discuss with the family
    - Infant's feeding
    - Enrollment in an early intervention program
    - Supplemental Security Income (SSI) and other programs that offer financial aid for extra costs of an infant with special needs
  - Tongue protrusion
    - Contributing factors include a relatively small oral cavity and upper airway obstruction with mouth breathing.
    - Behavior management techniques.
    - Oro-motor exercises.
  - Surgical and medical interventions to improve appearance and function
    - Tongue resection to improve speech; silicone implants to correct micrognathia; surgical interventions for eye appearance.
    - Discuss these interventions when they are considered by the family and be prepared to communicate the risks and benefits.
    - Tongue resection has not been observed to improve speech.

1–5 Years of Age

- Children with DS need annual health assessments.
  - At these office visits, inquire about the caregiver's concerns and review the health supervision issues for children with DS.

- Behavioral problems.
  - Many children who have DS do not fit the stereotype of being placid or compliant.
  - When the child seems to have a behavioral disorder
    - A thorough history should be obtained.
    - Parents should be asked about changes in environment or their expectations.
    - A complete physical examination should be performed.
    - Laboratory tests should be obtained, if warranted, to identify medical problems.
    - A trial of behavior management should be initiated for mild problems.
- Learning problems.
  - School learning problems require further evaluation.
    - They often come to the physician's attention when children are placed in mainstream classes.
  - Review current individualized education program (IEP).
    - Ensure that appropriate developmental testing has been completed.
    - Parents should have had an opportunity to provide information in the IEP process.
  - History should be reviewed thoroughly.
    - Ensure that parents' and teachers' expectations are appropriate for developmental age.
  - Identify medical problems that can affect learning and behavior.

5–13 Years of Age

- The annual health care visit incorporates all aspects of well-child health supervision.
- The primary care physician may receive many questions about behavior, nutrition, activity, and educational interventions.
- Social opportunities for children often become more challenging as they grow older, and the family will benefit from the advice of a trusted physician.

13–21 Years of Age

- Physical, emotional, and educational needs in adolescents require a special approach.
- During the annual health supervision visit, discuss with the family their adolescent's health, educational program, behavior challenges, and long-term plans for guardianship and care.

WHEN TO REFER

- A referral for parent-to-parent contact and local and national parent support organizations is helpful for prospective and new parents of a child with DS.
- In several states, physicians are legally mandated to connect parents to official information sources about DS.

FOLLOW-UP

1 Month–1 Year of Age

- Follow-up visits should assess
  - Emotional status of the parents
  - Adjustment of siblings
  - Effect of the infant on interfamilial relationships
- Review connection to early intervention services and their relationship to the needs of the infant and family.
- Growth and development.
  - Discuss feeding and nutritional intake carefully in the first visits and routinely in each health care visit.
  - Monitor weight and weight-for-height trends closely.
  - Plot growth parameters using standard growth charts of the Centers for Disease Control and Prevention (CDC) and the World Health Organization (WHO).
    - Previously used DS growth charts no longer reflect the current population; new DS-specific charts have been developed.
- Hearing.
  - Serous otitis media and associated fluctuating hearing loss are extremely common in young children with DS (50%–70%).
  - Infants who passed the newborn hearing screen should be reevaluated at 6 months of age and every 6 months thereafter until they are able to participate reliably in ear-specific testing with headphones, usually after age 4 years.
  - Any infant who fails a hearing screen should be evaluated for middle ear problems by an otolaryngologist comfortable with examining infants with stenotic ear canals.
- Vision.
  - Within the first 6 months of life, infants should be examined by a pediatric ophthalmologist for cataracts, nystagmus, and strabismus.
  - Lacrimal duct obstruction is common because of the craniofacial configuration.
  - Refer for surgical repair if obstruction is not resolved by 9–12 months of age.

- Thyroid disease.
  - Repeat TSH screening at ages 6 and 12 months and annually thereafter; hypothyroidism may be confused with common, unrelated findings in children with DS.

1–5 Years of Age

- Growth and development
  - A full history and physical examination should include attention to nutrition and growth.
  - Plot height, weight, and weight for height or body mass index (BMI) on the WHO or CDC growth charts.
  - Changes in diet may be recommended to ensure adequate calcium, vitamin D, iron, and appropriate fat content of the milk for child's weight for height or BMI.
  - For children who are picky eaters, are unable to chew meat, or do not have an adequate intake of iron-containing foods, a complete chewable multivitamin with iron may be crushed and added to food.
- Cardiac follow-up
  - Children with cardiac lesions should follow up with a pediatric cardiologist even after cardiac repair to monitor for residual lesions or pulmonary hypertension.
- Vision
  - Monitor for strabismus.
  - Ensure annual ophthalmologic examination until age 5 years.
  - Refractive errors and strabismus during preschool years is common.
- Hearing
  - Fluctuating hearing loss associated with serous otitis media is common in DS.
  - Tympanometry and a behavioral audiogram should be arranged every 6 months until the child is capable of ear-specific audiologic testing, usually around 6 years.
- Breathing and sleeping
  - Continue to ask about heavy breathing, snoring, restless sleep, daytime sleepiness, apneic pauses, uncommon sleeping positions, and behavior problems associated with poor sleep.
  - Strong correlation between obstructive sleep apnea, cognition, and behavioral problems.
- Teeth
  - A dental examination is recommended twice a year beginning at the first birthday.
  - Remind parents that delayed and irregular dental eruption and hypodontia are common.
- Sexual exploitation
  - Discuss with caregivers and model the use of accurate terms for genitalia and private body parts.
  - Teach child and family that the only reason for viewing or touching private body parts is for doctor visits or bathing and showering.
  - Discuss with caregivers the increased risk of sexual exploitation and educate them that most commonly, the perpetrators are people the child knows and trusts.
- Recurrence
  - Future pregnancy planning, recurrence risk, and resources for prenatal diagnosis should be provided during at least one visit when the child is 1–5 years of age.
- Atlantoaxial instability
  - Review signs and symptoms of spinal cord compression.
- Other topics
  - Questions about integrative therapies and eligibility for SSI, Medicaid, and other social service benefits
- Thyroid screening
  - Annually; sooner if symptoms of thyroid dysfunction occur
- Vaccines
  - All recommended vaccines for children with respiratory and cardiac problems
- Early intervention and education
  - Assess involvement of caregivers in the child's developmental program and needs of the child and family related to the child's strengths and weaknesses.
  - For children <3 years, review early intervention, including physical, occupational, and speech therapies.
  - Review the importance of caregiver involvement in the process.
  - IEP.
    - Discuss transition to preschool at the 30-month visit, as the family needs to understand the change from the individualized family service plan to the IEP in public education.
    - Review the current IEP for children >3 years to ensure the developmental program is appropriate and parents have an opportunity to provide input.

- Mainstream/regular classes.
  - School problems may come to the physician's attention more often when children are in mainstream classes.
  - Typically developing children are excellent role models, but additional supports in school are often required.
- School learning problems require further evaluation.
  - Review the history to ensure appropriate expectations and educational interventions for the child's developmental age and learning style.
  - Identify medical problems that can affect learning and behavior.

- Autism spectrum disorder (ASD) in DS
  - Increasing frequency in DS of symptoms attributable to ASD.
  - Assessment is most effective when done by a physician experienced in DS and ASD.
  - Consider diagnosis whenever social and communication skills lag significantly behind those expected for the child's general developmental level.
- Behavior problems
  - Ask about behavior problems.
  - Parents may not volunteer information about obstinacy or noncompliance.
  - If there are concerns, obtain a thorough history and ask parents about changes in the environment or their expectations.
  - Perform a complete physical examination and laboratory tests, if warranted, to identify medical problems.
  - Mild problems.
    - Initiate a trial of behavior management.
    - Consider diagnoses of ASD or physical abuse.
  - Severe behavior problems or persistent mild to moderate problems with no apparent medical cause.
    - Refer child to a behavior specialist familiar with DS.
    - Assess for celiac disease.

5–13 Years of Age

- Comprehensive well-child visit
  - Complete history
  - Review of systems
  - Physical examination
- Growth and development
  - Plot weight, height, and BMI on growth charts.
  - Monitor weight and activity because eating patterns for life can be best established in childhood.
- Hearing
  - Continue assessment every 6 months until the child is able to accomplish ear-specific testing (usually around age 6 years).
  - Test annually thereafter for development of optimal speech and communication.
- Vision
  - Evaluation by an ophthalmologist experienced in caring for children with disabilities every 2 years, or more often if problems are identified
- Other considerations
  - Evaluate the child for dermatologic problems.
  - Remind the family about cardiology follow-up as indicated and an annual dental evaluation.
  - Perform the physical examination with particular attention to myelopathic signs.
  - Review universal precautions for protection of the cervical spine during anesthetic, surgical, or radiographic procedures.
  - The primary care physician should be contacted immediately in the case of new onset of symptoms of myelopathy.
- Sports
  - Advise parents that some contact sports may place children at increased risk of spinal cord injury.
  - Consider with caution football, soccer, and gymnastics in older ages.
  - Avoid trampolines unless under direct professional supervision.
  - Special Olympics has specific screening requirements for participation by all athletes.
- Breathing and sleep
  - Review with caregivers any concerns about sleep.
    - Snoring
    - Restless sleep
    - Unusual sleep positions
    - Other concerns about sleep apnea
  - Discuss obesity as a risk factor for obstructive sleep apnea.

13–21 Years of Age

- Growth and development.
  - Evaluate nutritional status.
  - Plot height, weight, and BMI on a standard CDC growth chart.
  - Nutritional counseling and evaluation of activity.
- Include signs and symptoms of sleep disorder and the added risk of obesity for sleep apnea in the discussion.
- Annually review potential symptoms related to atlantoaxial instability and perform a careful examination for myelopathic signs.
- Continue to emphasize healthy lifestyle.
  - Special Olympics can provide excellent opportunities for activity.
- Discuss current educational planning.
- Explain the process of arranging for guardianship by age 18 years.
- Discuss financial planning, including enrollment in Medicaid and SSI.
- Recommend continuing speech and communication therapy.
- Living arrangements.
  - Most communities have a spectrum of community living facilities that range from small, heavily supervised group homes to apartments with minimal supervision.
  - Families need to make living arrangements 3–6 years before they anticipate the need because there is often a waiting list.
- Review behavior and social development.
  - Refer child with any acute deterioration in function for assessment.
  - Consider any history of possible seizures.
- Sexual health.
  - Discuss normal sexual development and behavior and provide understandable information on sexuality.
  - Provide family with information about contraception and prevention of sexually transmitted infections.
  - Discuss with girls the risk of having a child with DS.
  - Males are usually infertile, but instances of reproduction have been reported.
  - Girls should have routine gynecologic care and review of any premenstrual behavioral concerns and menstrual hygiene.
- Encourage increase in development of independent hygiene and activities of daily living.
- Counsel families about teaching their child to avoid tobacco and drug use.
- Additional medical considerations include
  - Cardiac history.
  - Evaluate older patients for acquired mitral valve and aortic valve disease, potential celiac disease, and annual TSH and hemoglobin screening.
  - Obtain ferritin and CRP screens for anyone at risk for iron deficiency.
  - Annual review of immunization status and influenza vaccine.
- Vision.
  - Eye examination every 3 years unless otherwise indicated
  - Special attention to ophthalmologic problems that typically occur after puberty, including cataracts, refractive errors, and keratoconus
- Hearing and teeth.
  - Remind family to obtain an ear-specific audiogram and dental examination annually or sooner if recommended.
- Adult care.
  - Discuss training for transition to adulthood.
  - For many patients, identifying providers of adult subspecialty care can be challenging.
  - Pediatric primary care physicians often continue to monitor adolescents into early adulthood.

COMPLICATIONS

Birth–1 Month of Age

- Congenital heart defects
  - ~50% of neonates with DS.
  - Obtain an echocardiogram and refer all neonates with an abnormal postnatal echocardiogram to a pediatric cardiologist.
- Gastrointestinal problems
  - 15% of neonates with DS.
  - May be evident very early in the newborn period or later in infancy.
  - Conditions that occur with increased frequency that should be evaluated and treated promptly include
    - Duodenal atresia
    - Tracheoesophageal fistula
    - Anorectal stenosis, atresia, or Hirschsprung disease
    - Malrotation

- Constipation.
  - Common and often associated with limited fluid intake, a restricted diet, and hypotonia.
  - Many neonates require treatment with a stool softener.
  - Hypothyroidism; gastroesophageal malformations, including stenosis; and Hirschsprung disease (2%) should be considered if constipation is refractory.

- Feeding problems
  - Most can breastfeed successfully.
  - Some will need supplementation with a bottle or tube until a successful nursing pattern is established.
  - Neonates who sleep for prolonged periods need to be awakened for feeds to ensure adequate caloric intake.
  - Ensure that nasal passages are clear and provide chin support for neonates with low tone.
  - Monitor weight gain in neonates with feeding problems.
  - If difficulty with nursing occurs, refer to a lactation consultant.
  - Refer neonates with the following conditions for a radiographic swallowing assessment:
    - Hypotonia and slow feeding
    - Choking with feeds
    - Recurrent pneumonitis
    - Other recurrent or persistent respiratory problems
    - Unanticipated failure to thrive
  - Use alternative feeding methods for neonates at risk for aspiration until they mature and the difficulty has resolved.
- Ophthalmologic problems
  - Assess neonates for presence of a red reflex.
  - Cataracts and congenital glaucoma occur with increased frequency and require an ophthalmologist experienced with neonates with DS.
- Hematologic abnormalities
  - Leukemoid reactions and transient myeloproliferative disorder (TMD) occur in ~10%.
    - Seen almost exclusively in newborns with DS
  - Polycythemia is relatively common.
  - Obtain a complete blood cell count and follow subspecialty recommendations for management.
  - TMD usually resolves spontaneously but carries a 10%–30% risk of later onset of leukemia.
  - Leukemia
    - Occurs in ~1%.
    - Counsel parents about possible early signs.
      - Easy bruising
      - Petechiae
      - Lethargy
      - Changes in feeding patterns
- Respiratory complications
  - Refer neonates with the following conditions to a pediatric pulmonary specialist:
    - Stridor
    - Noisy breathing
    - Upper airway obstruction with retractions
    - Wheezing
  - Intubation may be more difficult because of tracheal anomalies, including tracheal rings and small tracheal size.
  - Evaluate hearing at birth and complete a follow-up assessment by 3 months.
- Congenital hypothyroidism
  - Obtain TSH concentration to avoid missing congenital hypothyroidism, which occurs in ~1%.
  - Discuss management of neonates with abnormal thyrotropin or free thyroxine (T_4) levels with a pediatric endocrinologist.
- Atlantoaxial instability
  - Neurosurgical emergency requiring immediate referral and treatment.
  - Although it occurs in only 1.5% of neonates with DS, it can be life threatening and may cause irreversible disability.
  - Backward movement of the odontoid process of the axis, which may compress the spinal cord and result in signs and symptoms of cord compression.
    - Neck pain
    - Head tilt
    - Progressive weakness
    - Loss of bladder or bowel control
  - Take cervical spine positioning precautions to avoid excessive extension or flexion.
  - Neurologic examination reveals long-tract signs, such as increased deep-tendon reflexes in the lower extremities, a positive Babinski sign, and ankle clonus.

- Neck or radicular pain, weakness, spasticity or change in tone, gait difficulties, hyperreflexia, or change in bowel or bladder function should prompt plain cervical spine radiography in the neutral position.
  - Refer to a pediatric neurosurgeon or pediatric orthopedic surgeon experienced in managing a neonate with DS if plain cervical spine radiography in the neutral position is abnormal.
  - Routine radiographs of the cervical spine are no longer recommended.
- Adequate vertebral mineralization and epiphyseal development for accurate radiographic evaluation of the cervical spine does not occur until 3 years of age.
- Protect the cervical spine during any anesthetic, surgical, or radiographic procedure, but also reassure parents that normal care, including therapy to develop head control, is not dangerous and is important for development.

1 Month–1 Year of Age

- Obstructive sleep apnea
  - Refer infants with the following conditions to a pediatric sleep laboratory for a sleep study or polysomnogram:
    - Heavy breathing
    - Snoring
    - Restless sleep
    - Uncommon sleep positions
    - Frequent night awakening
    - Daytime sleepiness
    - Apneic pauses
    - Behavior problems that could be associated with poor sleep
  - Poor correlation between parent report of sleep symptoms and polysomnogram results; if possible, refer every infant with DS for a sleep study by age 4.

1–5 Years of Age

- Celiac disease
  - Symptoms include
    - Diarrhea
    - Protracted constipation
    - Slow growth
    - Unexplained failure to thrive
    - Anemia
    - Abdominal pain or bloating
    - Refractory developmental or behavioral problems
  - Patients with values outside of reference range should be referred for specialty assessment.

PROGNOSIS

- Mortality
  - Medical care involves particular diagnostic and consultative procedures because >50% have serious medical disorders.
  - First year of life holds the highest probability of death when an additional anomaly exists.
  - ~78% of infants with an additional anomaly survive, and 96% without an additional anomaly survive.
  - Survival of infants with cardiac malformations has improved, with only 8%–9% mortality now being reported in infants with DS and heart defects.
  - Leukemia as a cause of death is present in <10%.

DEFINITION

- Systemically administered drugs can cause almost any kind of rash.
- The types of skin reactions caused by drugs include
  - Most common
    - Exanthematous (measles-like) eruptions
    - Urticaria and angioedema
    - Erythema multiforme (EM)
      - An acute, self-limited eruption of symmetric erythematous macules and papules that can evolve into target lesions
      - Best viewed as a separate entity from Stevens-Johnson syndrome (SJS) and toxic epidermal necrosis (TEN)
  - Most severe
    - SJS
      - The major form of EM.
      - SJS and TEN, also known as Lyell syndrome, are 2 ends of a more severe process involving the acute onset of mucocutaneous necrosis.
      - Produces more focal skin necrosis than TEN, with ≥2 mucosal sites involved.
    - TEN
      - Extensive areas of epidermal necrosis and resulting denudation
  - Other
    - Erythema nodosum
    - Vasculitis
    - Photosensitivity reactions
    - Acneiform eruptions
    - Alopecia
    - Blistering disorders
    - Fixed drug eruptions
    - Lichenoid reactions
- Drug rash with eosinophilia and systemic symptoms (DRESS), formerly known as drug hypersensitivity syndrome.
  - Characterized by the clinical triad of fever, rash, and internal organ involvement (most commonly hepatitis, nephritis, pneumonitis, or myocarditis)

SIGNS AND SYMPTOMS

Exanthematous Eruptions

- Onset is not usually immediate but begins within 1–2 weeks after drug initiation.
  - Delayed reactions can occur as late as 1–2 weeks after drug has been discontinued.
- Eruption is generalized and consists of brightly erythematous macules and papules that tend to be confluent over large areas.
- Usually starts centrally on the trunk and proceeds distally.
  - Legs are typically the last to be involved and the last to clear.
  - Palms and soles are affected.
- Most drug eruptions are not accompanied by an elevation in body temperature.

Urticaria

- Hives are skin lesions that are recognized more easily than described.
- Hives appear as pink edematous papules and plaques that are most often scattered.
  - Often have pale or dusky centers and red borders
  - Frequently assume geographic shapes
  - Sometimes confluent
  - May be scattered but are usually generalized
- By definition, an individual hive is transient, lasting <48 hours, although new hives may develop continuously.
- Itching is almost always present.
- Obstructed airway or urticaria with significant edema suggests anaphylaxis.
- Fever, lymphadenopathy, and arthralgia often accompany hives in serum sickness reactions, for which the 2 most common causes are
  - Drugs, especially antibiotics
  - Viral hepatitis

DRESS

- Occurs within 2–6 weeks after initiating medication use.
- Clinical manifestations include
  - Fever early in the course
  - Diffuse macules
  - Papules or pustules that can progress to an exfoliative dermatitis mimicking SJS or TEN
  - Eosinophilia
  - Atypical lymphocytosis
  - Abnormal liver function test results
- The severity of skin involvement does not correlate with the extent of internal organ involvement.

Acute Generalized Exanthematous Pustulosis

- Characterized by the sudden onset of fever and multiple nonfollicular, subcorneal pustules over widespread erythema.
- Pustules are sterile and may clinically resemble pustular psoriasis.
- Affect the trunk and intertriginous areas; can also involve the face.

EM

- Characteristic EM lesions are noted a few days to 2 weeks following herpes simplex virus (HSV) orolabial or genital infections.
- Occasionally preceded by a febrile prodrome.
- Characterized by a variety of lesions, including
  - Erythematous plaques
  - Blisters
  - Targetoid lesions, sometimes confused with hives
    - Hives have only 2 zones of color: a central pale area surrounded by an erythematous halo.
    - The target lesion requires 3 zones: a central dark area or blister, surrounded by a pale zone, surrounded by a peripheral rim of erythema.
    - True target lesions are diagnostic for EM.
    - Seen more often on the palms and soles but may occur anywhere.
- Typically, EM is a strikingly symmetric eruption, most frequently seen on the dorsal hands and forearms and often involving palms, neck, face, and trunk.
- Lesions can be quite numerous, often exceeding 100.
- Lesions may appear grouped on the elbows or knees.
- Koebner phenomenon can be observed: after cutaneous trauma, target lesions may appear in the affected areas.
- Mild, discrete oral erosions occur in more than half of patients but are usually few in number and can be relatively asymptomatic.

SJS and TEN

- Usually preceded by a prodrome of ≤2 weeks of influenza-like symptoms followed by an abrupt onset of skin eruption.
- When drug related, eruption typically begins 7–28 days after initiation of the causative drug.
- Eruption is initially macular or morbilliform, tender, dusky, and erythematous and widespread in distribution.
- Skin sloughs off easily with minor friction (Nikolsky sign).
- Lesions gradually coalesce, and flaccid bullae develop that can extend laterally with central pressure (Absoe-Hansen sign).
- Bullae easily rupture and detach, leaving necrotic sheets of epidermis with a moist, bright red base.
- Similar lesions are also typically seen on mucous membranes, usually involving >2 mucosal sites.
- Thick, hemorrhagic crusts may appear on the lips.
- When ≤10% of the body surface area is involved, the eruption is termed *SJS*.
- When >30% is involved, it is termed *TEN*.
- When 10%–30% is involved, the eruption is termed *SJS-TEN overlap*.
- Constitutional symptoms include
  - Fever
  - Arthralgia
  - Malaise
  - Lymphadenopathy
  - Occasional symptoms of an upper respiratory infection
  - Rarely, hepatitis, nephritis, and myocarditis

DIFFERENTIAL DIAGNOSIS

- A general principle of dermatologic diagnosis: For any rash, think of drugs.

Exanthematous Eruptions

- Patients receiving >1 drug present a problem.
- The 2 variables to consider are
  - The temporal relationship between the administration of the drug and the onset of the rash
  - The likelihood that a given medication can cause a drug eruption
- Exanthematous eruptions have been reported in patients with Epstein-Barr virus (EBV) infection taking amoxicillin; their pathogenesis remains to be elucidated.
- Major differential diagnosis for exanthematous eruption.
  - Drug reaction
    - May be more erythematous and confluent, but not always.
    - Presence of eosinophilia favors a drug-related cause.
  - Viral exanthem
    - Clinically indistinguishable from a drug eruption
  - Toxic erythema (eg, scarlet fever), staphylococcal-induced scarlatiniform eruptions, Kawasaki disease (possibly)
    - Distinguishing features
      - Sandpaper-like roughened texture of the rash and mucous membrane involvement (scarlet fever and Kawasaki disease)
      - Fever
      - Focus of infection
      - Lymphadenopathy

- Postinflammatory desquamation from the skin of the hands and feet often follows the rash of toxic erythema, but this sign is not specific.
  - Drug eruptions and viral exanthems can involve hands and feet, particularly palms and soles in drug eruptions.

Urticaria

- Differential diagnosis of urticaria may be approached in 2 ways.
  - From the causes of hives per se
    - Usually the cause of hives cannot be determined; when found, it is usually drug-related.
    - Other causes include infection, physical stressors (eg, cold, pressure, sunlight), emotions, and foods.
- From consideration of the cause of lesions sometimes mistaken as hives.
  - Includes those seen in EM and juvenile idiopathic arthritis
  - In juvenile idiopathic arthritis, lesions are transient but differ in
    - Size (only 2–3 mm)
    - Color (typically salmon)
    - Timing (usually appear with fever spikes)

EM

- Skin reactions most commonly considered in the differential diagnosis are
  - Giant urticaria
    - Individual hives last <48 hours; the lesions in EM persist much longer.
  - Subacute cutaneous lupus erythematosus
  - Viral exanthems
    - Usually monomorphous and tend to be less red, more confluent, and more centrally distributed than EM
  - Vasculitis
    - Purpura is the distinguishing feature of vasculitic lesions.
  - Staphylococcal scalded skin syndrome (SSSS)
  - Other blistering eruptions
- Recurrent EM caused by HSV can be mistaken for photosensitive disorders because it can be triggered by significant sun exposure.
  - Polymorphous light eruption
  - Juvenile spring eruption

SJS and TEN

- The skin in SSSS is diffusely red and tender and exhibits a Nikolsky sign.

DIAGNOSTIC APPROACH

- Exanthematous eruptions
  - Patients receiving >1 drug present a problem.
  - The 2 variables to consider are
    - The temporal relationship between the administration of the drug and the onset of the rash
    - The likelihood that a given medication can cause a drug eruption
  - Exanthematous eruptions have been reported in patients with EBV infection taking amoxicillin; their pathogenesis remains to be elucidated.
  - Presumptive diagnosis is made based on clinical data.
- Urticaria
  - May be approached in 2 ways: from the intrinsic causes of hives, and from consideration of the cause of lesions sometimes mistaken as hives.
  - Drug history is the most important but also the most difficult to obtain, at least among outpatients.
  - Whenever a drug is suspected, persist in eliciting a medication history to be sure no drugs are overlooked.
  - Many patients and their parents consider over-the-counter medications unimportant.
    - Ask about specific medications to help jog their memories.
    - Nonsteroidal anti-inflammatory drugs cause hives in some and can aggravate them in others who have urticaria, regardless of its cause.
    - Aspirin can cause hives but is not widely used in children because of the risk of Reye syndrome.
- SJS and TEN
  - History of all medications.
  - The skin in SSSS is diffusely red and tender and exhibits a Nikolsky sign.
  - A skin biopsy helps distinguish SSSS from SJS.
  - Histologically, the level of the blister is intraepidermal in SSSS, whereas, in SJS and TEN, the blister is subepidermal.

LABORATORY FINDINGS

Exanthematous Eruptions

- No laboratory test can identify the responsible drug.
- Peripheral blood eosinophilia is sometimes present and may heighten suspicion for a drug reaction.
- For some drugs that can produce significant reactions in patients with certain human leukocyte antigen (HLA) types, genetic pre-therapy testing can predict which patients may be more likely to develop a drug reaction.

- The US Food and Drug Administration has recommended testing for HLA-B*1502, particularly in individuals of Asian ethnicity, before starting carbamazepine to avoid SJS.

Urticaria

- Urticaria may be accompanied by eosinophilia.
- In afebrile patients, laboratory tests are rarely helpful in eliciting a cause and are of no help in implicating a specific drug.
- To evaluate for hepatitis, obtain liver function tests in patients who have hives and fever.

DRESS

- Abnormal liver function test results

EM

- Laboratory evaluation usually is not helpful, although leukocytosis can be seen.
- For herpes simplex disease, if vesicular lesion is still present
  - Base can be scraped for HSV direct fluorescent antibody.
  - Fluid can be cultured for HSV or examined for multinucleated giant cells (Tzanck preparation).
  - When diagnosis is in doubt, a skin biopsy can be helpful in excluding conditions that mimic EM, such as lupus erythematosus or vasculitis.

SJS and TEN

- *Mycoplasma pneumoniae* infection can be confirmed further by
  - Cold agglutinin
  - Immunoglobulin M (IgM) antibodies to *Mycoplasma*
- Complete blood cell count may show leukocytosis.
- Urinalysis may show hematuria or proteinuria.

IMAGING

- SJS and TEN
  - Chest radiography is appropriate to screen for pulmonary involvement, including that caused by *M pneumoniae.*

DIAGNOSTIC PROCEDURES

- EM
  - When the diagnosis is in doubt, skin biopsy can exclude conditions that mimic EM.
    - Lupus erythematosus
    - Vasculitis
- SJS and TEN
  - Skin biopsy helps distinguish SSSS from SJS.
    - Histologically, the level of the blister is intraepidermal in SSSS.
    - In SJS and TEN, the blister is subepidermal.

TREATMENT APPROACH

Exanthematous Eruptions

- When an offending agent is identified, its use should be discontinued.
- If a patient is taking several drugs and the causative agent cannot be identified
  - Discontinue all nonessential medications.
  - Whenever possible, any remaining possible offending agents should be changed to alternative agents.
- Drug eruption may clear even when use of the offending agent is continued over 1–2 weeks; however, continued use of the drug is unwise if an alternative is available.

Urticaria

- Use of any suspected medication should be discontinued.

DRESS

- Immediate withdrawal of all suspected medications
- Supportive care of symptoms

EM

- No convincing evidence has been found that medical therapy favorably alters the course of EM.
- Treating a precipitating infection seems appropriate, even though no proof exists that it alters the course of the skin reaction.

SJS and TEN

- Use of any drug suspected of causing the reaction should be discontinued.
- Early transfer of the patient to an intensive care unit that can manage patients with severe skin burns also improves the ultimate outcome.
- Underlying infection should be treated.
- Supportive measures are vitally important.
  - Some experts recommend inserting a nasogastric tube on admission to maximize oral intake and decrease the risk of fluid overload.

SPECIFIC TREATMENTS

Exanthematous Eruptions

- Therapy is directed toward symptoms.
- Antihistamines for pruritus.

- Topical agents are usually confined to moisturizers during the desquamative phase of the reaction.
- Although topical steroids may be of some value in controlling pruritus, systemic steroids are rarely required.

Urticaria

- Symptoms are usually treated with second-generation antihistamines given on a regular, rather than an as-needed, schedule.
  - The safe maximum dose should be reached for one medication before adding additional oral antihistamines.
  - A short course of oral steroids may be used if antihistamines are unsuccessful.

DRESS

- Systemic corticosteroids are generally used in more severe cases involving significant exfoliative dermatitis, pneumonitis, or hepatitis.

EM

- Acyclovir begun after the onset of EM has not proven effective.
- Treatment of symptoms can be helpful.
  - Antihistamines may reduce the sensation of stinging and burning.
  - Antacid suspensions applied topically may alleviate oral ulcers.
- Children with frequently recurring EM caused by HSV may be good candidates for prophylactic acyclovir for 6–12 months.
- Systemic prednisone is sometimes used early in the course of severe EM.

SJS and TEN

- Erythromycin is recommended for *M pneumoniae* infections, although treatment may not alter the course of the skin disease.
- Supportive care.
  - Patients with severe oral involvement may be unable to eat and drink.
  - When skin involvement is extensive, transcutaneous fluid loss increases and replacement volumes must be adjusted accordingly.
  - Fluid replacement poses a unique challenge.
    - Surface area in patients with SJS and TEN may change, altering their fluid requirements.
    - Fluid intake may need frequent adjustment to maintain constant urine output while avoiding fluid overload, pulmonary edema, acute respiratory distress syndrome, and death.
    - Parenteral nutrition requires a central venous catheter line, with attendant risks of sepsis and other line-associated complications.
- Local therapy with antiseptics and dressings may help prevent secondary infection.
  - Patients who have severe involvement may require treatments similar to those for burn patients.
  - Silver nitrate–impregnated, biosynthetic, or biologic dressings have been shown to be particularly helpful without causing further epidermal detachment on removal.
- Systemic analgesics are used for pain.
- Topical anesthetics may be used intraorally to provide temporary relief for painful mouth lesions.
  - "Magic swizzle," containing one part each of diphenhydramine hydrochloride elixir, aluminum and magnesium hydroxide (eg, Maalox), and viscous lidocaine 2%, is one agent.
  - Be aware of the potential for systemic effects from lidocaine when ordering this agent for young children.
- Use of systemic steroids is controversial.
  - Steroids alone were reported effective in SJS.
  - Steroids and intravenous Ig (IVIG) have been reported to improve outcome in SJS, TEN, and SJS-TEN overlap syndrome; however, controlled prospective studies are needed.
- IVIG may hasten recovery by blocking the mediators of the apoptosis cascade that leads to epidermal destruction.
  - Doses of 2–3 g/kg given early in the course lead to more rapid cessation of epidermal detachment and lower mortality.

WHEN TO ADMIT

- DRESS/drug-induced hypersensitivity syndrome
- Acute generalized exanthematous pustulosis
- SJS
- TEN
- *M pneumoniae*-associated mucositis

WHEN TO REFER

- Recurrent EM
- Serum sickness–like reaction
- Drug hypersensitivity reactions with multiorgan involvement
- Unclear diagnosis

FOLLOW-UP

- DRESS
  - Patients with a history of DRESS should be followed for possible late manifestations, including recurrence of symptoms as well as development of hypothyroidism and type 1 diabetes mellitus.
- SJS and TEN
  - Early ophthalmic evaluation is warranted because of mucous membrane involvement.

COMPLICATIONS

Exanthematous Eruptions

- The complications of skin rashes are primarily cutaneous.
- Body heat increases and loss of water may be problems for patients who are seriously ill.
- Continuing use of offending agent can result in 2 types of consequences.
  - Cutaneous
    - Possible progressive worsening of the rash may result (rarely) in SJS or TEN.
  - Renal
    - Allergic interstitial nephritis is an uncommon development usually associated with penicillins and cephalosporins and only rarely with other drugs.

Urticaria

- In rare cases, can be accompanied by anaphylactic reactions

SJS and TEN

- Oral mucous membrane involvement can produce painful erosions, restricting intake and resulting in dehydration.
- Similar lesions in genital mucous membranes can cause dysuria and urinary retention.
- Internal organs are affected less often.
  - TEN can affect the respiratory system.
    - Patchy pulmonary disease
    - Bronchiolitis obliterans
    - Respiratory failure
  - TEN can affect the gastrointestinal tract.
    - Esophageal involvement can lead to dysphagia, malnutrition, and strictures.
    - Involvement of the small intestine can lead to abdominal pain and diarrhea.
- Conjunctivitis can produce residual ophthalmic complications, including
  - Keratitis sicca
  - Corneal ulceration or scarring
  - Permanent visual impairment
  - Blindness

PROGNOSIS

Exanthematous Eruptions

- Eruptions gradually clear after responsible agent is discontinued, usually 1–2 weeks.
- Eruption may worsen for several days after use of the offending drug has been stopped.

Urticaria

- Acute drug-induced urticaria that is IgE mediated usually clears within 24–48 hours after the offending agent is discontinued.

EM

- Patients with mild forms of EM usually recover uneventfully within 4 weeks.
- EM recurs in 10%–20% of patients and is particularly common in patients with milder disease precipitated by recurrent HSV infection.

SJS and TEN

- Disease can last as long as 4–6 weeks in patients with severe involvement.
- Patients with these disorders may die because of extensive loss of skin integrity or complications from involvement of other organ systems.
  - Mortality rates of ≤30% have been reported.
  - A severity-of-illness score for TEN predicts a patient's risk of death according to the presence or absence of 7 risk factors.
    - Age >40 years
    - Presence of cancer
    - Heart rate >120 beats/min
    - Extent of skin involvement >10% on admission
    - Blood urea nitrogen level >28 mg/dL
    - Serum glucose level >252 mg/dL
    - Serum bicarbonate level <20 mmol/L

PREVENTION

Exanthematous Eruption

- If a responsible drug has been identified
  - The patient should be advised about the allergy.
  - The medical record should be clearly labeled, even though not all of these reactions reflect true allergy.

Urticaria

- If a specific agent has been identified, the patient must be alerted to avoid that drug.
- Most hives are IgE mediated and a repeat challenge with the responsible drug is more likely to result in an anaphylactic response than it would following a morbilliform eruption.

EM

- Children with frequently recurring EM caused by HSV may be good candidates for prophylactic acyclovir for 6–12 months.

Drug Interactions and Adverse Effects

DEFINITION

- The term *adverse drug reaction* (ADR) describes adverse medication effects and drug interactions.
- *Drug interaction* is a generic term used when the efficacy or toxicity of a medication is changed by another medication or food.
- An ADR is caused by the interaction between the drug or drugs and patient-specific characteristics, some of which may be unknown prior to the medication administration.
- ADRs generally are
  - Type A: a predictable, but excessive, pharmacologic effect caused by an increase in drug concentration or effect, *or*
  - Type B: an unpredictable toxic or immunologic (eg, allergy, anaphylaxis) response
- ADRs depend on factors such as
  - Patient pharmacogenomics
  - The disease being treated
  - Medications being used
- In an ADR, there is a causal link between the medication and the adverse event that must be determined by investigating
  - The time relationship
  - Pathophysiology of the drug
  - Competing causes
  - Response of the patient to removal or reduction in the dose

HISTORY

- Evaluating the potential for drug–drug interactions can be challenging.
- Useful tools for tailoring interaction alerting are
  - The Office of the National Coordinator drug–drug interaction list
  - The list from Leapfrog Computerized Physician Order Entry testing standard
- Interaction data are predominantly adult-based.
  - Despite assumptions that pediatric data would be similar, analysis of 24 drug pairs studied in adults and children indicates that the level of drug–drug interaction in children can be higher, similar, or lower than in adults.
- A systematic approach to a suspected ADR can clarify and identify the source.
  - Include the presence or absence of systemic signs to form an initial clinical impression and a differential diagnosis.
  - Obtain a complete history of the drugs taken, including types, doses, and duration.
    - Include over-the-counter medications and herbal and naturopathic compounds.
  - Obtain a detailed description of the symptoms and signs, including onset, localization, and evolution.

PHYSICAL EXAMINATION

- Perform a physical examination, including skin and mucosal membranes.
- Assess vital signs and laboratory parameters that suggest warning signs, such as
  - Hypotension
  - Fever
  - Skin blisters or bullae
  - Complete blood cell count for lymphopenia or thrombocytopenia
  - Eosinophilia
  - Liver transaminases
  - Renal function panel

DIAGNOSTIC PROCEDURES

- In the absence of a definitive diagnosis, defining the reaction as highly probable, probable, possible, unlikely, or almost excluded can be helpful.
- Criteria for a *highly probable reaction* include the following principles of causality:
  - Temporal relationship
  - Recognized response to the suspected drug
  - Improvement after drug withdrawal
  - Reaction on rechallenge
- A *probable reaction* includes
  - A temporal relationship
  - Recognized response to the suspected drug
  - Improvement after drug withdrawal
- A *possible reaction* requires only a temporal relationship.
- Genetic variations may provide some explanation for significant differences in drug metabolism that can lead to toxicity and harm.
  - Genetic testing has the potential to predict medication efficacy and toxicity.

TREATMENT APPROACH

- Before administering a medication to a patient, it is essential to verify the "5 rights."
  - Right patient
  - Right medication
  - Right time
  - Right dose
  - Right route
- Even when all 5 rights have been observed, a potentially life-threatening ADR may still occur.

- Recognition is a key first step when an ADR occurs.
  - Allows measures to be taken to minimize recurrence, if possible
- Data captured in nurse charting may be inappropriately minimized as unavoidable side effects.
  - One example is pruritus with morphine labeled as a minor side effect.
    - This assessment could lead to compounding reactions (eg, risk of delirium if diphenhydramine is prescribed).
  - With recognition of the initial ADR, alternative narcotics could be chosen and such risks minimized.
- Life-threatening ADRs merit documentation (eg, trimethoprim-sulfamethoxazole–induced toxic epidermal necrolysis or Stevens-Johnson syndrome).
- When documenting ADRs, note
  - Severity of reaction
  - Causal association between medication use and event
  - Dosing variables
- Inpatient records with details often do not translate well to outpatient care.
  - Clear communication with the family, other practitioners, and the patient about the ADR and its causality and implications is often overlooked.
- ADRs associated with new drugs *must* be reported.
  - Serious ADRs that occur at a frequency of ≤1 case per 1,000 population are unlikely to be detected prior to drug approval.
  - This is especially true in pediatrics, so pediatric ADR reporting is even more crucial.
  - The US Food and Drug Administration (FDA) is interested in any (unexpected) adverse drug experience that is not listed in the current product labeling.
    - Report through the online MedWatch: The FDA Safety Information and Adverse Event Reporting Program.
    - Drug and drug class safety warnings issued by the FDA are available at www.fda.gov/medwatch/index.html.

PREVENTION

- Documenting ADRs in the medical record is helpful in preventing subsequent harm to patients.
  - High likelihood for recurrence

D

Table 1. Drugs Frequently Prescribed to/Substances Frequently Taken by Children Known to Inhibit or Induce Drug Metabolism

Inhibitor	Enzyme Inhibited
Clarithromycin, erythromycin	CYP3A4
Itraconazole, ketoconazole, voriconazole	CYP3A4
Esomeprazole, pantoprazole, omeprazole	CYP2C19
Grapefruit juice	CYP3A4
Inducer	**Enzyme Induced**
Phenobarbital	Multiple CYPs
Rifampin	Multiple CYPs
Dexamethasone	CYP2D6
Carbamazepine	Multiple CYPs
Phenytoin	Multiple CYPs
Ethanol	CYP2E1
St John's wort	CYP3A4s

Abbreviation: CYP, cytochrome P450.

From de Wildt SN, Tibboel D, Leeder JS. Drug metabolism for the paediatrician. *Arch Dis Child.* 2014;99(12):1137–1142. Reprinted with permission.

Dysmenorrhea

DEFINITION

- Dysmenorrhea (painful menstruation) is a syndrome characterized by
  - Varying degrees of crampy, lower abdominal pain
  - Nausea
  - Vomiting
  - Urinary frequency
  - Low back pain
  - Diarrhea
  - Fatigue
  - Thigh pain
  - Nervousness
  - Dizziness
  - Sweating
  - Headache
- Pain typically begins just after menses and lasts ~1–2 days.
  - Can also begin 1–2 days before onset of menses and last up to 4 days into menstruation.
  - Cramps may be more severe among teenagers who smoke.

HISTORY

- Assessment of a teenager with dysmenorrhea should include
  - Complete menstrual history
  - Timing of cramps or pain
  - Episodes of missed school or other activities
  - Ability to participate in social events
  - Presence of nausea, vomiting, diarrhea, dizziness, or other symptoms
  - Medications used, including doses
  - Factors that improve or worsen symptoms
  - Family history of dysmenorrhea or endometriosis
- Consider the possibility that the patient has another, unstated purpose in seeking care.
  - Reluctance to attend school
  - History of physical or sexual abuse
  - Significant psychosocial problems
  - Secretly sexually active and seeking to obtain oral contraceptive pills (OCPs) for the purpose of contraception
- Causes of secondary dysmenorrhea
  - Can usually be excluded by careful history and physical examination.
  - Underlying pathologic conditions should be anticipated when
    - Pain begins after 20 years of age.
    - There is a history of surgery related to the genitourinary or gastrointestinal tract.
    - Pain is dull and constant rather than crampy.

PHYSICAL EXAMINATION

- Physicians differ in their opinions on what examination is necessary to evaluate a patient with dysmenorrhea; in general
  - For a non-sexually active teenager with mild to moderate menstrual cramps relieved by nonsteroidal anti-inflammatory drugs (NSAIDs)
    - Only an external genital examination to rule out hymenal abnormalities is indicated.
  - If dysmenorrhea is unresponsive to NSAIDs
    - Initiate OCPs for a few cycles without first performing a pelvic examination.
  - For a sexually active teenager or for one who is having significant pain that is unresponsive to NSAIDs
    - A thorough pelvic examination is necessary.
    - If pelvic examination is not possible, rectoabdominal examination will provide some useful information about the presence of masses or adnexal tenderness.

DIFFERENTIAL DIAGNOSIS

Primary Dysmenorrhea

- Most affected teenage girls have primary dysmenorrhea.
  - Not associated with pelvic or other pathologic conditions
- Secondary dysmenorrhea always should be considered when the patient is evaluated.

Secondary Dysmenorrhea

- Endometriosis
  - Functional endometrial glands and stroma are located outside the normal anatomic location in the uterus.
  - Therapy with NSAIDs and OCPs fails.
  - A family history of endometriosis can often be elicited.
  - Signs and symptoms include
    - Pain may be acyclic rather than cyclic.
    - Menstrual bleeding may be irregular.
    - Gastrointestinal symptoms may be present.
    - May be associated with dyspareunia, tenesmus, and rectal pain.
    - Most adolescents generally have normal examinations.
      - Endometriosis can be difficult to detect on clinical grounds alone.
  - Some studies of teenagers with chronic pelvic pain show that 25%–38% of those undergoing laparoscopy have endometriosis.

- In other studies, 52%–73% of teenagers with chronic pelvic pain have evidence of endometrial implants.
- May be difficult to manage.
- Increases risk for infertility.

- Pelvic inflammatory disease (PID)
  - Can cause dysmenorrhea acutely.
  - Women often develop chronic pelvic pain as a consequence.
  - Even with assurances of confidentiality, some young women may still not admit to sexual activity.
    - Clinicians must maintain a high index of suspicion if historical and physical examination findings suggest PID.
  - A pelvic examination that reveals cervical motion tenderness, adnexal tenderness, or masses strongly suggests PID.
  - Should be treated according to standard antibiotic regimens (see Sexually Transmitted Infections).
  - Follow-up is critical; once infected, young women are at risk for
    - Further episodes of PID
    - Chronic pelvic pain
    - Ectopic pregnancy
    - Infertility
- Outflow tract obstruction
  - Teenagers with a history of genital tract surgery, including abortions, may have outflow tract obstruction.
  - A variety of müllerian anomalies with incomplete obstruction of the outflow tract also produce dysmenorrhea.
  - Depending on the type of obstruction, a pelvic mass may be palpable.
  - Outflow obstruction is possible (eg, a uterus with a blind horn) if
    - The cervical os is stenotic.
    - The cervix or uterus feels atretic or abnormally shaped.
- Endometrial polyps or fibroids
  - Rare in women <20 years
  - Should be anticipated if menstrual bleeding is
    - Heavy
    - Prolonged
    - Associated with the passage of clots
  - Unclear whether these entities alone cause dysmenorrhea

LABORATORY EVALUATION

- If sexually active, evaluate for
  - Sexually transmitted infections
  - Pregnancy

IMAGING

- Pelvic ultrasonography
  - May be useful in defining uterine and vaginal abnormalities associated with obstruction
  - Not helpful in the detection of pelvic or abdominal adhesions or endometriosis

DIAGNOSTIC PROCEDURES

- Confirmation of endometriosis requires laparoscopy.
  - Should be performed by a gynecologist experienced in evaluating adolescents because the lesions of endometriosis in adolescents may differ from the typical lesions seen in adults

TREATMENT APPROACH

- Treatment of primary dysmenorrhea is likely to include drug therapy.
- Valuable opportunity to teach the patient about her body.
  - The patient may not understand fully the physiologic mechanisms of menstruation.
  - The patient may have inaccurate beliefs passed on from mother to daughter.

SPECIFIC TREATMENT

Primary Dysmenorrhea

- NSAIDs
  - Teenagers who have very mild discomfort benefit from almost any analgesic.
  - Prostaglandin synthetase inhibitors in the form of NSAIDs are the treatment of choice for most young women with dysmenorrhea.
  - Dosage and timing vary from patient to patient.
    - Establishing prior use of specific medications as well as doses is important, given that most patients use them suboptimally.
      - In one study, 57% of adolescents used medications less often than the maximal daily frequency.
      - Advising patients of the range of correct doses is important.
  - Most effective if started at the first sign of menstrual bleeding.
    - Women who experience significant nausea with menses may benefit from starting treatment at the earliest symptom of menses, even before bleeding occurs.

- Some need medication only for part or all of the first day of menstruation; others require medication for ≥4 days.
- Ibuprofen (200–800 mg every 6–8 hours) and naproxen sodium (550 mg immediately and then 275 mg every 6–8 hours) are highly effective.
- Mefenamic acid blocks the effect of prostaglandin at the end-organ level and inhibits its production.
  - Can be used in an initial dose of 500 mg, followed by 250 mg every 6 hours.
  - Note that there is a black box warning.
- Celecoxib, a cyclooxygenase inhibitor, has been shown to be effective.
  - 200 mg every 12 hours.
  - Intestinal bleeding and cardiovascular events limit use.
- Response to different NSAIDs varies.
  - If the patient does not respond to a particular NSAID (eg, ibuprofen), another (eg, naproxen sodium) should be tried.
- Between 70% and 80% of girls will respond to NSAID therapy.

- OCPs
  - OCPs used in the same way as for contraception usually provide relief.
  - OCPs work by suppressing ovulation and decreasing endometrial prostaglandin production.
  - Patients should be told that 2–3 cycles may elapse before maximal effect.
  - If the patient is sexually active, OCPs can be continued on a routine basis.
  - For the non-sexually active teenager, therapy can be reassessed at 6- to 12-month intervals.
  - After 3 cycles, adolescent patients using OCPs with 20 mcg of ethinyl estradiol and 100 mg of levonorgestrel experienced significant relief of dysmenorrhea compared with those using placebo.
- Other hormonal contraceptives
  - In a study of adolescent girls using a contraceptive patch, dysmenorrhea
    - Decreased in 39%
    - Increased in 11%
    - Resulted in no change in 50%
  - Depot medroxyprogesterone acetate (DMPA).
    - Used to prevent ovulation and menstrual flow when OCPs are not tolerated or estrogen is contraindicated
  - Extended oral contraceptive regimen in which OCPs are taken for up to 12 consecutive weeks, followed by 1 hormone-free week.
  - Continuous OCPs have been well accepted and shown to eliminate menses, thereby reducing dysmenorrhea.
  - DMPA and extended OCP regimens
    - Decrease dysmenorrhea.
    - Decrease the frequency of menses.
- Other treatments
  - Some authorities remain skeptical of alternative treatments, and efficacy is unproved.
  - Other experts recommend
    - Heat
    - Pelvic exercise
    - General exercise
    - Biofeedback
    - Relaxation therapy
    - Massage
    - Vitamin E
    - Various herbal remedies
  - Magnesium has been shown to be beneficial in some studies.
  - Patient should be encouraged to
    - Exercise.
    - Eat a well-balanced diet.
    - Decrease stress.
    - Decrease caffeine consumption.
    - Stop smoking, if applicable.

WHEN TO REFER

- The clinician feels uncomfortable prescribing OCPs for the treatment of primary dysmenorrhea.
- The patient does not respond to NSAIDs and OCPs.
- The clinical presentation or course suggests that the patient has secondary rather than primary dysmenorrhea.
- The patient is sexually active and the clinician feels uncomfortable performing a pelvic examination.

WHEN TO ADMIT

- With PID, some clinicians recommend hospitalization of adolescents for treatment.
- Others recommend hospitalization under some, but not all, circumstances (see Sexually Transmitted Infections).

FOLLOW-UP

- Reevaluate after 2–3 menstrual cycles to determine the effectiveness of the treatment.

DEFINITION

- *Dysphagia* is defined as difficulty with swallowing.
  - Derives from the Greek *dys* (difficulty) and *phagia* (to eat).
  - It is not synonymous with *odynophagia,* which refers to painful swallowing.

HISTORY

- Emphasis should be placed on
  - Birth history
  - Neurodevelopmental history
  - Medical comorbid conditions
  - Detailed feeding history
    - Current diet
      - Texture
      - Route of administration
      - Meal duration
      - Specific food aversions
    - Age at which oral feeding commenced
    - Exposure to taste and textures during sensitive periods
    - Aversive experiences
    - Method of delivering tube feeds
      - Prolonged tube feeding in infancy or childhood can lead to long-term feeding difficulties.
- General symptoms
  - Feeding difficulties
  - Food refusal
  - Failure to thrive
  - Sensation of food stuck in the throat or chest
- Additional symptoms
  - Drooling
  - Difficulty initiating swallowing
  - Change in dietary habits
  - Aversion to certain food textures
  - Unexplained weight loss
  - Change in voice
  - Recurrent coughing
  - Noisy breathing during feeding
- Symptoms of specific dysphagias
  - Oral phase
    - Failure to initiate or maintain sucking
    - Prolonged feeding time
    - Drooling
  - Oral hypersensitivity
    - Exaggerated gag reflex
    - Difficulty making the transition to textured foods
    - Sensitivity to touch in and around mouth
  - Oral hyposensitivity
    - Retaining food in the mouth
    - Increased drooling
  - Pharyngeal phase
    - Coughing
    - Choking
    - Noisy breathing during feeding
    - Nasopharyngeal reflux
  - Esophageal phase
    - Spitting up or vomiting
    - Irritability or arching during feeding
    - Preference for liquid food
    - Sensation of food stuck in the throat

PHYSICAL EXAMINATION

- Document any orofacial malformation.
  - Mechanical or obstructive factors generally result in dysphagia for solids.
  - Micrognathia and glossoptosis seen in Pierre Robin sequence may cause feeding difficulty.
  - Cleft lip and palate, including submucous cleft, are important causes of dysphagia.
  - Choanal stenosis may cause difficulty feeding in newborns because of obligate nasal breathing.
- Neurologic examination.
  - Assess muscle tone and strength.
  - Evaluate cranial nerve function.
  - Dysphagia for liquids is more pronounced in patients with neurologic disorders.
- Clinical feeding evaluation.
  - Performed by an experienced occupational therapist or speech pathologist.
  - Includes assessment of
    - Posture
    - Positioning
    - Oral structure and function
    - Patient motivation
    - Interaction between the infant and feeder
  - A variety of foods, positions, and adaptive utensils may be used during the examination.

DIFFERENTIAL DIAGNOSIS

Utility of Specific Symptoms

- Specific symptoms observed during feeding can help identify the underlying disorder.
  - Gagging, coughing, or emesis
    - Structural or neurologic disorder
  - Repeated swallowing after feeding, fussiness, crying, regurgitation, or nausea
    - Gastroesophageal reflux disease (GERD)
    - Requires further investigation

Oropharyngeal Dysphagia

- Oropharyngeal dysphagia should be considered in young children with
  - Recurrent aspiration
  - Apparent life-threatening events
  - Recurrent pneumonia
  - Chronic lung disease
  - Unexplained respiratory symptoms
    - Coughing
    - Chronic congestion
    - Recurrent choking

Causes of Dysphagia

- Preterm birth
  - Birth weight <10th percentile for gestational age is a risk factor for dysphagia and feeding difficulties.
- Congenital abnormalities of the nasal and oral cavity
  - Cleft lip or palate
  - Choanal atresia or stenosis
  - Craniofacial anomalies
    - Apert syndrome
    - Crouzon syndrome
    - Möbius syndrome
    - Pierre Robin sequence
    - Treacher Collins syndrome
  - Congenital nasal masses
    - Dermoids
    - Encephaloceles
- Congenital anomalies of the larynx, trachea, and esophagus
  - Laryngomalacia
  - Laryngeal clefts
  - Laryngeal stenosis and webs
  - Vocal cord paralysis
  - Tracheoesophageal fistula
  - Esophageal atresia
  - Esophageal duplication
- Vascular rings
  - Double aortic arch
  - Right aortic arch with left ligamentum from a descending aorta
  - Innominate artery tracheal compression
- Infection
  - Acute pharyngitis or tonsillitis
  - Peritonsillar and retropharyngeal abscesses
  - Epiglottitis
  - Esophagitis (cytomegalovirus, herpesvirus, *Candida albicans*)
- Inflammatory causes
  - Esophagitis secondary to GERD
  - Eosinophilic esophagitis
    - Should be considered in the differential diagnosis of children with unexplained
      - Oral aversion
      - Feeding difficulties
      - Poor weight gain
- Neurologic or neuromuscular disorders
  - Hypoxic-ischemic encephalopathy
  - Head trauma
  - Cerebral palsy
  - Congenital malformations
    - Arnold-Chiari malformation
    - Absent corpus callosum
  - Degenerative diseases of white and gray matter
  - Brain stem tumors
  - Syringomyelia
  - Infantile spinal muscular atrophy (Werdnig-Hoffmann disease)
  - Diseases of the neuromuscular junction
    - Myasthenia gravis
    - Guillain-Barré syndrome
    - Botulism
  - Muscle disorders
    - Congenital myopathies
    - Mitochondrial diseases
    - Glycogen storage diseases
    - Congenital muscular dystrophy
    - Myotonic dystrophy
- Trauma
  - External trauma
  - Intubation injury
  - Caustic ingestion
- Neoplasms
  - Hemangioma
  - Lymphangioma
- Miscellaneous
  - Foreign body aspiration
  - Achalasia (esophageal motor dysfunction)
  - Epidermolysis bullosa
  - Nonorganic feeding disorders

LABORATORY EVALUATION

- Complete blood cell count
  - Useful as a screening test for infectious or inflammatory conditions
- Serum protein and albumin
  - Useful for nutritional assessment

- Chromosomal karyotyping, metabolic analysis, specific DNA tests
  - May be required for a specific diagnosis as directed by physical and neurologic examination

IMAGING

- Chest radiography
  - Suspected pneumonia or chronic lung disease.
  - Persistent pulmonary infiltrates on chest radiograph may be better elucidated by high-resolution chest computed tomography.
- Magnified airway radiography
  - Infants or children with recurrent stridor or upper airway obstruction
- Computed tomography or magnetic resonance imaging of the brain
  - May be especially helpful in patients with suspected central nervous system injury or structural abnormalities
- Upper gastrointestinal barium study
  - Assess anatomic or structural abnormalities.
    - Strictures
    - Fistulae
    - Masses
    - Intestinal rotational anomalies
  - Usually more sensitive than endoscopy in the evaluation of suspected
    - Achalasia
    - Vascular rings, which appear as a persistent indentation of the esophagus
- Videofluorographic swallowing study (VFSS)
  - Gold standard for assessment of the oral and pharyngeal stages of swallowing.
    - Also known as the *modified barium study*
  - Conducted jointly by a radiologist and a speech pathologist or occupational therapist.
  - The child drinks or eats foods mixed with barium while radiographic images are observed and recorded.
  - Provides evidence of all categories of oropharyngeal swallowing dysfunction.
    - Inability or excessive delay in initiation of pharyngeal swallowing
    - Aspiration of food
    - Nasopharyngeal regurgitation
    - Residue of food in the pharyngeal cavity after swallowing
  - Allows for testing of the efficacy of compensatory
    - Dietary modifications
    - Postures
    - Swallowing maneuvers

DIAGNOSTIC PROCEDURES

- Fiber-optic endoscopic evaluation of swallowing (FEES)
  - Permits observation of the pharyngeal phase of swallowing.
    - Laryngeal penetration
    - Aspiration
  - A fiber-optic endoscope is introduced into the nose and advanced into the laryngopharyngeal area.
    - Swallowing assessment is performed with liquids and a variety of textures, if developmentally appropriate.
    - Typically, dye is added to the food to provide better visualization and to determine residual pooling of food versus saliva.
  - Combined with laryngopharyngeal sensory testing.
    - Has shown that patients with a higher laryngopharyngeal sensory threshold are more likely to experience laryngeal penetration and aspiration during a feeding assessment.
    - Ability to initiate airway closure with stimulation demonstrates airway protection.
    - FEES and sensory testing may be particularly valuable for evaluation of swallowing safety in children who refuse to ingest adequate amounts of barium to perform VFSS.
- Esophagogastroduodenoscopy
  - Confirms or establishes diagnosis of dysphagia of esophageal origin.
    - When appropriate, used to implement therapy
  - Endoscopic and histologic features are required for the diagnosis of eosinophilic esophagitis.
    - Normal appearance of the esophagus during endoscopy does not exclude histopathological esophagitis.
    - Subtle mucosal changes, such as erythema and pallor, may be observed in the absence of esophagitis.
    - During endoscopy, esophageal biopsy should be performed to detect microscopic esophagitis and to exclude causes of esophagitis other than gastroesophageal reflux.
  - Particularly useful in evaluating suspected
    - Strictures
    - Webs
    - Mucosal inflammatory lesions
    - Specific infections
- Esophageal manometry
  - Standard test for disorders of esophageal motility

- Especially useful in
  - Establishing a diagnosis of achalasia
  - Detecting esophageal motor abnormalities associated with autoimmune diseases
- Esophageal pH probe study
  - Valid and reliable measure of acid reflux
    - Establishes the presence of abnormal acid reflux.
    - Determines whether a temporal association exists between acid reflux and frequently occurring symptoms.
    - Assesses the adequacy of therapy in patients who do not respond to treatment with acid suppression.
    - Most centers are replacing pH monitoring with combined multiple intraluminal impedance and pH monitoring.
      - Superior to pH monitoring alone for evaluation of the temporal relation between symptoms and GERD
- Scintigraphy
  - Useful in the evaluation of gastric emptying.
  - Can demonstrate episodes of aspiration detected during a 1-hour study or on images obtained up to 24 hours after the test feeding is administered.
  - Its role in diagnosing GERD in infants and children is unclear.
- Children with suspected neuromuscular disorders may need
  - Electromyography
  - Nerve conduction studies
  - Muscle biopsy

TREATMENT APPROACH

- Goals.
  - Reduce aspiration.
  - Improve ability to eat and swallow.
  - Optimize nutritional status.
- Detect and treat
  - Surgically or endoscopically treatable structural abnormalities
  - Inflammatory conditions
    - Reflux esophagitis
    - Eosinophilic esophagitis
  - Infections
  - Underlying systemic conditions
- Management of associated disorders.
  - Associated disorders may also need to be specifically managed.
- Management often involves a multidisciplinary approach.

SPECIFIC TREATMENT

Normalization of Posture and Tone

- Head and trunk control are crucial to the development of oral motor skills.
  - Children with neurologic abnormalities frequently have poor head control and poor trunk stability.
- As a basis for improved oral motor function, occupational and physical therapy can be used to improve
  - Head control
  - Neck and trunk tone
  - Posture

Adaptation of Food and Feeding Equipment

- Change the attributes of food and liquids.
  - Bolus volume
  - Consistency
  - Temperature
  - Taste
- Adjustments in feeding schedule
  - May be beneficial for children receiving continuous tube feeds with supplemental food orally.
  - The feeds can be changed gradually to bolus feeds to stimulate the child's appetite.
- Rate of feeding
  - Should be paced to allow sufficient time to swallow before giving another bite
- Bottle or utensils
  - May be changed according to the child's needs

Oral Motor Therapy

- Focuses on improving the oral phase of feeding
- May include stimulation with
  - Stroking
  - Stretching
  - Brushing
  - Icing
  - Tapping
  - Vibrating areas of the face and mouth

Nutritional Support

- The child's nutritional needs must be met for adequate growth.
  - Supplemental feedings through a nasogastric tube or a percutaneous endoscopic gastrostomy may be necessary.
    - The presence of a feeding tube is not a contraindication to therapy.

- Many children with feeding disorders have neurologic or anatomic abnormalities that cannot be corrected, making oral feeding difficult or unsafe.

Synchronized Neuromuscular Electrical Stimulation to Cervical Swallowing Muscles

- Improves oral intake in adults.
- Helps restore normal swallowing mechanism in adults.
- Empirical data are lacking to support its use in children.

WHEN TO REFER

- Referral is warranted
  - When symptoms are persistent
  - When the cause of dysphagia is unclear
  - With evidence of aspiration
- Referral to a pediatric dysphagia center, if available, provides the most complete method to establish a diagnosis and develop a management plan.
  - Members of the team vary from center to center and usually include
    - Gastroenterologist
    - Otolaryngologist
    - Physical medicine and rehabilitation specialist
    - Surgeon
    - Occupational therapist
    - Pediatric dietitian

WHEN TO ADMIT

- Severe feeding difficulties
- Malnutrition
- Failure to thrive
- Dehydration
- Aspiration

FOLLOW-UP

- Patients who are undergoing therapy for dysphagia should be monitored closely for appropriate weight gain.

COMPLICATIONS

- Undernutrition
- Failure to thrive

PREVENTION

- Early recognition, diagnosis, and intervention are necessary, especially in children born preterm, those with anatomic abnormalities, and those with neuromuscular disorders.

Dyspnea

DEFINITION

- Dyspnea is the feeling of not being able to satisfy air hunger.

HISTORY

- The child's age is important.
  - Various disorders occur with different frequencies at different ages.
- Obtain a complete description of the dyspnea.
  - Onset
    - — Sudden, suggesting inhaled foreign body or lung collapse
    - — Evolving over time, suggesting asthma or diabetic ketoacidosis
  - Duration
  - Frequency of attacks
  - Any identifiable trigger event
- Quantify the severity of the dyspnea.
  - Ask how daily activities are restricted by shortness of breath.
- Ask whether the dyspnea changes according to patient's position.
  - Dyspnea that is worse when the patient lies with the affected side down.
    - — Suggests unilateral lung disease
  - Dyspnea that worsens when the patient is recumbent.
    - — Suggests left ventricular failure, obstructive airway disease, or muscle weakness
  - Dyspnea in the upright position that is relieved by lying down.
    - — Suggests intracardiac, vascular, or parenchymal lung shunts
- Ask about associated symptoms.
  - Cough
  - Wheezing
  - Sputum production
  - Pleuritic pain
- History (patient and family) of
  - Allergies
  - Respiratory illness
  - Medications
  - Environmental exposure

PHYSICAL EXAMINATION

- A complete physical examination is necessary, with special attention to the respiratory and cardiac systems.
- Observe for retractions in the following areas:
  - Suprasternal
  - Infrasternal
  - Intercostal
  - Subcostal
  - Supraclavicular
- Observe for tachypnea.
  - Measure the respiratory rate.
- Observe for nasal flaring and grunting.
- Observe the abdominal and intercostal muscles during expiration.
- Assess the ratio of inspiration to expiration.
  - In normal respiration, they are of equal length.
  - If inspiration and expiration are equally prolonged, a fixed obstruction may be present.
  - If inspiration is longer than expiration, extrathoracic obstruction may be present.
    - — Inspiratory stridor is likely to be present in this setting.
  - If expiration is longer than inspiration, intrathoracic obstruction may be present.
    - — If the large airways are involved, rhonchi are present.
    - — If the small airways are involved, the patient will be wheezing.
- Observe for signs of chronic lung or heart disease.
  - Barrel chest
  - Clubbing
  - Cyanosis
  - Paradoxical pulse
- Palpate the chest.
  - Tactile fremitus can be a sign of pulmonary consolidation or pleural effusion.
- Percuss the chest.
  - Assess for effusions, consolidation, and abnormal diaphragmatic excursion.
- Auscultate the chest.
  - Listen for rales, rhonchi, and wheezing.
  - Assess for changes in whispered pectoriloquy and egophony.
- Look for cardiac findings that indicate pulmonary hypertension.
  - Accentuated P_2
  - Paradoxical splitting of S_2
  - A third heart sound
  - Pulmonary ejection click
  - Right ventricular heave

DIFFERENTIAL DIAGNOSIS

Pulmonary Causes of Dyspnea

- Pulmonary disease that causes dyspnea can be classified as obstructive, restrictive, or vascular.

Obstructive Pulmonary Disease

- Obstructive pulmonary disease is characterized by airway narrowing.
- Newborns
  - Choanal atresia or stenosis
  - Dermoid cyst
  - Encephalocele
  - Nasolacrimal duct cyst
  - Hemangioma
  - Vocal cord paralysis
  - Pierre Robin sequence
  - Ankyloglossia (tongue-tie)
  - Pertussis
  - Tracheal stenosis (post-intubation)
- Infants
  - Foreign body
  - Vascular ring
  - Tracheal web
  - Bronchiolitis
  - Asthma
  - Cystic fibrosis
  - Bronchomalacia
  - Pyogenic thyroid
  - Accessory thyroid
- Children and adolescents
  - Foreign body
  - Asthma
  - Adenopathy
    - Lymphoma
    - Systemic lupus erythematosus
    - Tuberculosis
    - Sarcoidosis
  - Croup
  - Epiglottitis
  - Retropharyngeal abscess
  - Enlarged tonsils or adenoids
  - Cystic fibrosis
  - Anaphylaxis
  - Tumors
    - Laryngeal
    - Vocal cord
    - Tracheal
    - Mediastinal
  - Vocal cord polyp
  - Laryngeal trauma
  - Supraglottitis
  - Bacterial tracheitis
  - Diphtheria
  - Ingestion of caustic substance
  - Crack cocaine
  - Trauma
  - Exposure to environmental or occupational inhaled toxin

Restrictive Pulmonary Disease

- Restrictive pulmonary disease is characterized by reductions in lung volume and compliance, usually with rapid, shallow breathing.
- Newborns
  - Hyaline membrane disease
  - Hypoplastic lungs
  - Pulmonary agenesis
  - Eventration of the diaphragm
  - Meconium aspiration
  - Pneumonia
    - Group B streptococci
    - Gram-negative organisms
  - Diaphragmatic paralysis
  - Osteogenesis imperfecta
  - Central nervous system depression
    - Hypoxia
    - Congenital
    - Maternal drugs
  - Congenital myasthenia gravis
  - Aspiration
  - Pulmonary edema
    - Septicemia
    - Congenital heart disease
- Infants
  - Pneumonia
    - Bacterial
    - Viral
    - Aspiration
  - Bronchopulmonary dysplasia
  - Wilson-Mikity syndrome
  - Hamman-Rich syndrome (acute interstitial pneumonitis)
  - Pulmonary edema
  - Infant botulism
  - Congenital lobar emphysema
- Children and adolescents
  - Parenchymal
    - Pneumonia
    - Hypersensitivity pneumonitis
    - Systemic lupus erythematosus
    - Scleroderma
    - Granulomatous disease
    - Fibrosis
    - Toxin inhalation

- Smoke inhalation
- Drugs (eg, antineoplastic agents, narcotics)
- Pneumothorax
- Pneumomediastinum
- Pulmonary edema
  - Congestive heart failure
  - Sepsis
  - Intracranial disease
  - Croup
  - Epiglottitis
- Pulmonary infarction
- Fat embolus
- Carcinoma

- Pleural effusion
  - Pneumonia
  - Cancer
  - Cardiac disease
  - Hepatic disease
  - Renal disease
  - Rheumatologic disease
  - Hypoproteinemia
- Skeletal
  - Kyphoscoliosis
  - Ankylosing spondylitis
  - Pectus excavatum
  - Crush chest injury
- Neuromuscular
  - Cord transection
  - Myasthenia gravis
  - Muscular dystrophy
  - Multiple sclerosis
  - Guillain-Barré syndrome
  - Obesity-hypoventilation syndrome
  - Toxins

Vascular Pulmonary Disease

- Vascular pulmonary disease is characterized by a decrease in the size of the pulmonary vascular bed.
- May be accompanied by pulmonary edema and pleural effusion.
- Newborns and infants
  - Persistent pulmonary hypertension of the newborn
  - Microthrombi from severe respiratory distress
- Children and adolescents
  - Persistent left-to-right shunting, with consequent pulmonary hypertension and intimal hyperplasia
  - Thromboembolic disease
  - Vasculitis resulting in obliteration
  - Emphysema resulting in destruction

Nonrespiratory Causes of Dyspnea

Exercise-Induced Dyspnea (EID)

- If EID is severe or occurs after only minimal exertion, further evaluation is warranted.
- Asthma is the most common cause.
- Other causes of EID include
  - Vocal cord dysfunction
  - Exercise-induced laryngomalacia
  - Exercise-induced hyperventilation
  - Skeletal deformities (eg, scoliosis) that restrict the airway

Cardiac Disease

- Congenital structural anomalies in the heart
- Pump failure (myocarditis or cardiomyopathy)
- Restrictive pericarditis
- Arrhythmia

Hematologic Disease

- Severe anemia
  - Chronic or acute
  - Congenital or acquired
- Decreased oxygen binding by hemoglobin
  - Carbon monoxide poisoning
  - Methemoglobinemia
  - Cyanide poisoning
- Blood hyperviscosity
  - Polycythemia
  - Markedly elevated leukocyte or platelet counts

Metabolic Disease

- Disorders that increase the body's rate of metabolism and oxygen consumption (eg, hyperthyroidism or fever).
- Disorders that increase production of hydrogen ion and carbon dioxide (eg, diabetic ketoacidosis or aspirin poisoning) can result in dyspnea-like breathing.
- Muscle enzyme deficiencies can result in increased acid production and decreased work tolerance.
- In chronic renal failure, the kidney cannot remove acid from the blood, resulting in dyspnea.

Obesity

- Dyspnea occurs because of increased metabolic requirements for a given amount of work.

Pregnancy

- Dyspnea is normal during pregnancy.
  - Rarely severe and rarely occurs at rest
  - Begins early in pregnancy and resolves by last trimester
  - No other signs or symptoms of cardiac or pulmonary disease

- Dyspnea as a result of cardiac disease in pregnancy begins during the second half of pregnancy and is worst during the seventh month.

Intravenous Drug Use

- Heroin can cause bronchospasm.
- Heroin and other opioids can precipitate pulmonary edema.
- Infection in intravenous drug users include
  - Community-acquired pneumonia is the most common.
  - Opportunistic pulmonary infections.
  - Tuberculosis.
  - Bacterial endocarditis.
- Talc granulomatosis from injection of dissolved opioid tablets.

Psychogenic Causes

- Stress or hysteria
  - Dyspnea does not improve with rest and may even worsen.
  - Patients often complain of chest pain and sigh more frequently than normal.
  - Physical examination is usually benign, although paradoxical adduction of the vocal cords has been reported.

LABORATORY EVALUATION

- Most useful laboratory tests include
  - Complete blood cell count
  - Peripheral blood smear
  - Arterial blood gas measurement
    - Normal with mild obstructive pulmonary disease.
    - Hypoxemia is the first abnormality seen in progressive obstructive disease, followed by hypocapnia and then hypercapnia.
    - Hypoxemia and hypocapnia is the typical pattern in restrictive pulmonary disease.
    - Hypoxemia and hypercapnia in vascular pulmonary disease from reduced blood flow through the lungs.
    - Despite tissue hypoxia, children with anemia may not be hypoxemic on blood gas measurement.

IMAGING

- Chest radiography
  - Obstructive pulmonary disease
    - May reveal hyperinflation
  - Restrictive pulmonary disease
    - Decreased lung volume
    - Pleural thickening and effusions
    - Increased interstitial markings
    - Parenchymal consolidation
    - Skeletal deformities
    - Abnormal movement of the diaphragm
  - Pulmonary edema
    - Increased right ventricular size
    - Enlargement of the pulmonary artery
    - Alterations in pulmonary blood flow

DIAGNOSTIC PROCEDURES

- Use pulse oximetry as a quick, noninvasive means to measure arterial saturation.
- Pulmonary function tests may be useful but may not be immediately available for an acutely ill patient.
- Laryngoscopy, bronchoscopy, and esophagoscopy may be useful to identify a radiolucent foreign body.

TREATMENT APPROACH

- Severe dyspnea is a medical emergency.
  - If not treated promptly, the child may progress to respiratory failure and death.
- Dyspnea in chronic illness.
  - There may be no satisfactory therapy for the underlying disease.
  - Relieving the dyspnea can still improve functional ability and quality of life.

SPECIFIC TREATMENT

Severe Dyspnea

- Assess the adequacy of the airway.
- Remove foreign bodies, if present.
- Administer oxygen until the cause of dyspnea is known.
- Treat bronchospasm with β-agonists.
- In the post-emergent period, evaluate the efficacy of ventilation.
  - If the child cannot effect adequate ventilation, consider the need for mechanical ventilation.
- Assess the heart, peripheral circulation, intravascular volume status, and blood oxygen-carrying capacity.
  - Treat with vasopressors, fluids, blood transfusion, or diuretics, as appropriate.

Dyspnea in Chronic Illness

- Sedatives and narcotics can be used to reduce minute ventilation.
  - Usually administered orally or by injection
  - Also effective when delivered by nebulization
- Prostaglandin inhibitors and β-agonists may blunt the feeling of dyspnea without affecting ventilation.
- Theophylline may improve diaphragmatic contractility.
- Continuous supplemental oxygen reduces ventilatory drive.
- Noninvasive positive pressure ventilation assists fatigued or dysfunctional respiratory muscles and helps keep small airways open.
- Exercise and proper nutrition can maintain or increase inspiratory muscle mass.

Psychogenic Dyspnea

- Calm reassurance.
- Occasionally, mild sedation.
- Psychotherapy and hypnosis may be required to reduce stress and gain insight into the cause of the dyspnea.

WHEN TO REFER

- Chronic pulmonary disease
- Congenital or acquired heart disease
- Metabolic disease
- Conditions requiring endoscopy or surgical procedures

WHEN TO ADMIT

- Respiratory failure
- Impending respiratory failure
- Hypoxia while breathing room air

PROGNOSIS

- Prognosis depends on the underlying cause.

Dysuria

DEFINITION

- Any discomfort with urination
- Refers particularly to pain or burning during urination
- Generally stems from irritation of the bladder or the urethra

HISTORY

- Dysuria is rarely an isolated symptom; a thorough history is essential.
- Ask about associated symptoms, specific to the urinary tract and nonspecific, more general symptoms.
  - Symptoms specifically related to the genitourinary system
    - Hematuria
    - Discharge
    - Malodorous urine
    - Frequency
    - Urgency
    - Refusal to void
    - New-onset nocturnal enuresis
    - Daytime incontinence
  - More general, nonspecific symptoms suggestive of an infection or systemic inflammatory condition
    - Fever
    - Conjunctival injection
    - Oral or genital ulcers
    - Joint pain
    - Generalized rash
- Ask about exposure to
  - Detergents
  - Perfumed soaps
  - Bubble baths
  - Ointments
  - Underwear fabric
- History of voiding dysfunction can help elucidate diagnosis of dysfunctional elimination syndrome.
  - Timing of toilet training
  - Nighttime enuresis
  - Constipation and withholding maneuvers
- Sexual history.
  - Ask adolescents about sexual activity and safety practices.
  - Ask about sexual trauma, masturbation, or abuse.
    - Response may be inaccurate because child does not recall or may deliberately deny.
- Ask about family history of nephrolithiasis or other genitourinary problems.

PHYSICAL EXAMINATION

- Perform thorough physical examination.
  - Presence of fever may indicate inflammation or upper urinary tract infection (UTI).
    - Pyelonephritis: fever >38.5°C (101.3°F) usually present.
    - Cystitis and urethritis of any cause do not usually produce significant fever.
  - Inspect skin for vesicles or target lesions.
  - If there is a history of voiding dysfunction, observe the lower back for midline defects such as sacral cyst, fistula, and hair tuft.
- Neurologic examination.
  - Evaluate lower extremity strength and reflexes.
  - Elicit the bulbospongiosus reflex.
- Abdominal examination.
  - Flank or suprapubic mass suggests urethral obstruction.
  - Costovertebral tenderness suggests pyelonephritis.
  - Suprapubic tenderness often accompanies cystitis.
- Examine the genital area and observe for
  - Discharge
    - Cheesy discharge is found in candidiasis.
    - Greenish discharge is associated with gonorrhea and pelvic inflammatory disease (PID) if accompanied by lower abdominal tenderness.
  - Scratch marks suggesting contact dermatitis or chemical irritation
  - Labial adhesions
  - Urethral prolapse from urethral orifice
  - Whether foreskin is age-appropriately retractable in uncircumcised males
  - Size and location of meatus for hypospadias or stenosis

DIFFERENTIAL DIAGNOSIS

UTI

- UTI is the most common cause of dysuria.
- Patient may report suprapubic pain.
- Fever, if present, is usually low grade with lower tract infection.
- Girls <2 years and boys of any age should be evaluated for congenital anatomic abnormalities after the first UTI.
- Pyelonephritis is suggested by the presence of systemic features.
  - Fever >38.5°C (101.3°F), vomiting, diarrhea
  - Flank pain
  - Costovertebral tenderness

Urethritis

- May result from
  - Infection
  - Trauma
  - Chemical irritation
  - Foreign body
- Urethral discharge or blood spots on the underwear may be present.
- Infectious urethritis in children is uncommon.
  - Sexually transmitted infections are the major cause in adults and adolescents.
  - *Neisseria gonorrhoeae* and *Chlamydia trachomatis* in a child should prompt consideration of sexual abuse.

Irritants and Trauma

- Local irritants may produce mild erythema.
  - Bubble baths
  - Detergents
  - Perfumed soaps
- Localized trauma may cause dysuria.
  - Foreign bodies
  - Sexual abuse
  - Voluntary sexual activity
  - Masturbation

Meatal Stenosis

- Relatively common following circumcision in boys.
- Typically an upward, deflected, difficult-to-aim urinary stream.
- May be accompanied by
  - Dysuria
  - Increased frequency
  - Delayed bladder emptying

Dysfunctional Voiding

- Neuropathic disorders affecting innervation of muscles involved in coordinated micturition
  - Spina bifida
  - Transverse myelitis
  - Spinal cord trauma
- Non-neuropathic disorders
  - All other causes of lack of coordination between bladder, bladder outlet, and pelvic floor muscles
  - Dysfunctional elimination syndrome if patient is also constipated
    - History should focus on timing of toilet training, bed-wetting, and daytime incontinence.

Systemic Inflammatory Disease

- Stevens-Johnson syndrome
- Reactive arthritis (Reiter syndrome)
- Behçet syndrome

Less Common Causes of Dysuria

- Labial adhesions in prepubertal girls are generally asymptomatic unless they cause secondary infection.
- Urethral strictures.
  - Acquired as a result of urethral instrumentation, trauma, or inflammation.
  - Congenital strictures are rare.
  - Symptoms include dysuria, infection, or a weak urinary stream.
- Urethral prolapse.
  - Complete protrusion of urethral mucosa beyond the meatus in girls.
  - Rare, occurring primarily in girls of black or Hispanic background or low socioeconomic status.
  - Dysuria accompanied by gross hematuria or blood spotting on underwear.
- PID.
  - Primarily in sexually active adolescent girls
  - Should raise suspicion of sexual abuse in prepubertal girls
  - Presents with abdominal pain (See Sexually Transmitted Infections.)
- Vulvovaginitis.
  - Rare and presents with erythema of the vaginal mucosa.
  - Associated vaginal discharge varies from clear to white to green and odorless or foul-smelling.
  - Mostly seen in sexually active adolescents.
  - Usually caused by sexually transmitted pathogens; poor hygiene or allergies may play a role.
    - Group A *Streptococcus*.
    - Anaerobic bacteria.
    - *Candida* species following antibiotic treatment or diabetes.
    - Herpes simplex may present with erythema alone.
- Balanitis and balanoposthitis.
  - Inflammatory lesions of the glans penis (balanitis) or glans and prepuce (balanoposthitis).
  - Most common in uncircumcised young boys.
  - Infection results from smegma trapped beneath the foreskin.
  - May be a result of trauma, allergies, or poor hygiene.

- Hypercalciuria.
  - Frequency
  - Urgency
  - Gross or microscopic hematuria
  - Dysuria
  - Family history of urolithiasis

LABORATORY EVALUATION

- Urine culture for suspected UTI
- Urethral smear and urine culture if urethritis is suspected
- If vaginal discharge or erythema of vaginal mucosa is present, examine sample for
  - pH.
  - Wet preparation.
  - Potassium hydroxide.
  - Gram stain.
  - Culture.
  - Consider screening for herpes simplex.

IMAGING

- Cystourethrography or cystoscopy can confirm a diagnosis of urethral strictures.

TREATMENT APPROACH

- The overall goal is to identify the cause of dysuria and treat appropriately.

SPECIFIC TREATMENT

- Cystitis and UTI: See UTI section.
- Antibiotic treatment of vaginitis: See Vaginal Discharge.
- Dysfunctional voiding from neurologic conditions: See Anuria and Oliguria.
- PID and sexually transmitted infections: See Sexually Transmitted Infections.
- Labial adhesions.
  - Separation of adhesion and topical estrogen to prevent readhesion
- Balanitis and balanoposthitis.
  - Warm soaks.
  - Oral or local antibiotic therapy.
  - Topical steroids may alleviate inflammation.
- Meatal stenosis.
  - Refer to a pediatric urologist.
  - Surgical meatotomy is the recommended treatment.
- Urethral prolapse.
  - Medical treatment
    - Sitz baths
    - Antibiotics
    - Topical estrogen
  - Surgical repair if medical treatment fails

WHEN TO REFER

- Voiding dysfunction
- Nephrolithiasis
- Girls <2 years with a UTI for the first time
- Boys of any age with a UTI or with meatal stenosis
- Genitourinary tract anomalies

WHEN TO ADMIT

- Systemic inflammatory or infectious cause of dysuria
- Suspicion of sexual abuse

Edema

DEFINITION

- Edema is the accumulation of fluid in the interstitial tissues.
  - Results from disruption of forces that control normal fluid movement out of and into capillaries.
  - May result from many different disease states.
  - Diagnosis of the underlying cause is generally apparent, but it may be subtle.
  - Intervention may initially need to be supportive.
    - Once a patient is stable, efforts to treat the underlying cause of the edema should be pursued.
    - Services of a specialist may be required.

HISTORY

- A detailed history must be obtained to discover the cause of the edema.
- The time course of the edema—whether its onset is recent or chronic—is particularly important.
  - If chronic, parents and child may report
    - Weight gain
    - Tight clothing
    - Snug-fitting shoes
  - Parents may have attributed findings to normal growth.
- History of a recent illness, such as pharyngitis, is important for the diagnosis of glomerulonephritis.
- Other systemic complaints may be present, which may indicate the presence of heart failure and pulmonary edema.
  - Shortness of breath
  - Tachypnea
  - Cough
- Ascites, a form of localized edema, is seen with liver failure or cirrhosis and with some congenital liver malformations.
- The child's nutritional status should be assessed.
  - Malnutrition may result in hypoalbuminemia, which can result in edema.

PHYSICAL EXAMINATION

- Edema may be generalized or localized.
  - If localized, edema is very apparent when it affects an extremity.
    - Deep-vein thrombosis
    - Cellulitis
    - Burn
  - Edema may be more occult.
    - Pulmonary edema from left-ventricular heart failure
    - Ascites from liver disease
  - Generalized edema may include scrotal or labial edema.
    - Findings related to generalized edema may depend on whether the patient has been lying down (sacral edema) or standing (feet and lower legs).
    - Chronic edema may result in bedsores.
- Physical examination should begin with close observation of the vital signs.
  - Tachypnea may indicate pulmonary edema.
  - Increased blood pressure may be present in glomerulonephritis and renal failure.
  - Fever and localized edema may be present with cellulitis.
  - Periorbital edema is generally found with nephrotic syndrome and glomerulonephritis.
  - Crackles or rales may indicate the presence of pulmonary edema.
  - A gallop may indicate heart failure.
  - With ascites, the following conditions may be present:
    - Abdominal distention
    - Shifting dullness
    - A fluid wave
  - A distinction may be made between pitting and nonpitting edema.
    - *Nonpitting edema* is often the result of lymphedema.
    - *Pitting edema* is the result of increased membrane permeability, increased hydrostatic pressure, or decreased oncotic pressure.

DIFFERENTIAL DIAGNOSIS

- Renal causes of edema
  - Nephrotic syndrome.
    - Proteinuria with low serum albumin is highly suggestive of nephrotic syndrome.
  - Glomerulonephritis.
    - Assess for the presence of
      - Red cell casts
      - Hematuria
      - Cola-colored urine
    - C3 levels may be needed to help distinguish between the types of glomerulonephritis.
  - Elevated blood urea nitrogen may suggest chronic renal injury.
  - Congenital renal anomalies.
    - Small or malformed kidneys on ultrasound and clinical findings of renal failure.
    - Bilateral hydronephrosis in an infant boy with edema may be the result of posterior urethral valves.

- Children with undiagnosed reflux nephropathy may have severe hydronephrosis and renal failure.

- Cardiovascular causes of edema
  - Congestive heart failure
  - Deep-vein thrombosis
  - Embolic disease
  - Vasculitis
  - Constrictive pericarditis
- Hematologic causes of edema
  - Severe anemia, especially in a newborn
    - Hemolysis from ABO blood type or Rh incompatibility
    - Glucose-6-phosphate dehydrogenase deficiency
- Endocrine or metabolic causes of edema
  - Thyroid disease
  - Starvation
  - Hereditary angioedema
- Gastrointestinal causes of edema
  - Cirrhosis
  - Protein-losing enteritis
  - Cystic fibrosis
  - Celiac disease
  - Enteritis
  - Lymphangiectasis
  - Lymphatic abnormalities
  - Milk protein allergy
  - Inflammatory bowel disease
- Hypoalbuminemia without proteinuria suggests
  - Synthesis defect found with chronic liver disease
  - A protein-losing enteropathy

LABORATORY EVALUATION

- Initial testing may include
  - Urinalysis
  - Complete blood cell count
  - Electrolytes with blood urea nitrogen and creatinine
  - Liver function tests (liver enzymes as well as serum albumin, prothrombin time, and partial thromboplastin time)
    - Clotting studies if venous thrombosis is suspected, especially if no predisposing factor, such as an indwelling catheter, is present
  - Lipid studies and cholesterol
  - Thyroid function tests
- Results may suggest further testing.
  - With proteinuria, C3, C4, and antinuclear antibody (ANA) may be indicated.
    - Low C3 and C4 with elevated ANA suggest lupus nephritis.
  - Testing for fecal fat is appropriate if intestinal malabsorption is suspected.
    - α_1-Antitrypsin may be helpful for diagnosing protein-losing enteropathy.
  - With angioedema, whether hereditary or acquired, levels of C1 esterase inhibitor are low.
  - When serum albumin is normal, depending on the clinical circumstance, thyroid function tests may be required.

IMAGING

- Doppler ultrasound
  - Suspicion for venous thrombosis
- Chest radiograph and electrocardiogram
  - Suspicion for heart failure
- Renal ultrasound examination
  - Hydronephrosis with congenital anomalies, such as dysplastic kidneys or posterior urethral valves

DIAGNOSTIC PROCEDURES

- When serum albumin is normal, depending on the clinical circumstance, electrocardiogram may be required.

TREATMENT APPROACH

- Initial management involves determining whether the patient should be admitted to the hospital.
- Ongoing management depends on the underlying cause of the edema.

SPECIFIC TREATMENT

General

- Most patients with renal disease benefit from a low-sodium diet.
- Fluid restriction may help but should be used cautiously on an individual-patient basis in consultation with a nephrologist.
- Diuretics may be needed but should be used cautiously.
- If plasma volume is decreased, fluid expansion with colloid followed by diuretics may be necessary.

Anemia

- Severe anemia may need to be treated with transfusion.
  - A hematologist should be consulted if the cause of the anemia is not readily apparent.

Ascites

- A low-sodium diet is generally helpful.
- Diuretics may be beneficial, especially spironolactone.
- When possible, treating the underlying cause of the ascites is critical.

Heart Failure

- Treating heart failure may require inotropic medications.
  - Digoxin
  - Dobutamine
  - Angiotensin-converting enzyme inhibitor may help with afterload reduction.
  - If congenital heart disease is the cause of heart failure, surgical repair of the underlying structural lesion is the ultimate treatment.

Venous Thrombosis

- When venous thrombosis is present, anticoagulation therapy may be indicated.
  - Consultation with a hematologist and possibly a vascular surgeon may be necessary.
  - In the absence of an obvious predisposing factor, investigation for an underlying coagulopathy is appropriate.

Enteropathy

- For patients with enteropathy, treatment depends on the cause.
  - A gastroenterologist should be consulted.

Hypothyroidism

- Generally, myxedema is found with hypothyroidism.
  - Responds to treatment with thyroid hormone replacement

WHEN TO REFER

- Many disorders that cause edema may require the assistance of a specialist.
- Referral to a specialist should be considered for edema if evidence exists of
  - Liver disease (ie, ascites)
  - Renal disease (glomerulonephritis, nephritic syndrome)
  - Anemia
  - Protein depleting enteropathy or increased fecal fat with malabsorption with secondary hypoalbuminemia
  - Heart failure

WHEN TO ADMIT

- Many of the causes of edema are serious medical problems that require admission.
  - Initial approach may be for support.
  - Once a diagnosis is established and the patient is stable, further treatment usually continues on an outpatient basis with assistance of a specialist.
- Any of the following conditions may require admission:
  - Respiratory distress
  - Heart failure
  - Tachypnea
  - Renal failure
  - Acute glomerulonephritis or nephrotic syndrome
  - Emergent admission for oliguria from renal failure
  - Edema caused by previously unrecognized cirrhosis
  - Localized edema that results from venous thrombosis or lymphatic obstruction
  - Anemia severe enough to require a transfusion

PROGNOSIS

- Prognosis depends on the underlying cause and the appropriateness of treatment.

DEFINITION

- Encopresis (soiling)
  - Intentional or involuntary passage of feces into the clothing by children with a developmental age >4 years
- Retentive encopresis
  - Leakage of fecal material involuntarily from an impaction
- Non-retentive encopresis
  - Passage of normal bowel movement (BM) into underwear rather than the toilet

SIGNS AND SYMPTOMS

- Patient or parent reports
  - Constipating medication
  - Constipating diet
- Findings on physical examination
  - Chronic anal fissure
  - Perianal cellulitis
  - Delayed linear growth
    - Indicates hypothyroidism
  - Mass on rectal examination
  - Dilated rectum packed with stool (often 6–10 cm across)
    - Impacted stool usually has the consistency of wet clay.
  - Rectal ampulla empty, rectum tight
    - Hirschsprung disease
- Retentive encopresis
  - Palpable abdominal mass
    - Usually involves only the rectosigmoid area but may extend throughout the colon.
    - Midline, suprapubic, irregular, and movable.
    - Can be missed if the rectus abdominis muscles are not relaxed.
    - Protuberant abdomen may be caused by backup of gas and stool.
  - Fecal matter protruding from the anal opening
- Non-retentive encopresis
  - Normal abdominal examination
  - Rectal vault contains
    - Stool of normal caliber
    - Nothing, if the child has evacuated recently

DIFFERENTIAL DIAGNOSIS

- Retentive encopresis
  - Symptoms of constipation.
  - Soiling many times per day.
  - Small stools.
  - Loose stools.
  - Need for laxatives, suppositories, or enemas.
  - Abdominal mass present.
  - Abdominal distention.
  - The anal canal may be full.
  - Rectum packed with stool.
  - Periodic pain or crying with BMs.
  - Blood on the toilet tissue.
  - Passage of a huge BM that clogs the toilet.
  - Posturing that suggests deliberate holding back.
- Non-retentive encopresis
  - No constipation
  - Soiling once per day
  - Stool of normal size
  - Stool of normal consistency
  - No need for laxatives, suppositories, or enemas
  - No abdominal mass
  - No abdominal distention
  - Empty anal canal
  - Normal rectum

DIAGNOSTIC APPROACH

- Thorough history to distinguish between retentive and non-retentive encopresis.
- Review diet.
  - Milk products
  - Fruit juice
  - Fiber
- Question child's use of the toilet.
  - How many times per day?
  - Is sitting spontaneous or prompted by parents or teachers?
- If the stool pattern is unknown, the parent should be sent home with a soiling diary to complete for the child.

LABORATORY FINDINGS

- Urinalysis
  - For nitrite and pyuria
    - To screen for urinary tract infection, especially if associated with enuresis
- Culture for group A *Streptococcus* if abnormal perianal erythema is present
- Thyroid function tests, if warranted

IMAGING

- Plain film, post-voiding, supine abdominal radiography
  - If needed to determine whether the patient is impacted (eg, severe obesity, abdominal fullness but empty rectum)
  - For a sexually abused child who might be emotionally traumatized by a rectal examination
  - If child refuses rectal examination

- Radiologic findings
  - Grossly dilated rectum
  - Granular stool
  - Increased stool in the transverse and descending colon
- Barium enema
  - Only if Hirschsprung disease is strongly suspected
  - For children with repeated treatment failures, to reassure the family (and physician) that some rare diagnosis has not been overlooked

DIAGNOSTIC PROCEDURES

- Rectosigmoid manometric study
  - In suspected Hirschsprung disease

CLASSIFICATION

- Encopresis (soiling)
- Retentive encopresis
- Non-retentive encopresis

TREATMENT APPROACH

- Retentive and non-retentive encopresis must be addressed separately.
- Retentive encopresis.
  - Bowel clean out: hyper-phosphate enemas (1 daily for 2 or 3 days) to remove impaction (other option: oral clean out using high-dose stool softeners).
  - Maintenance medication: mineral oil or polyethylene glycol for 3–6 months to keep the stools soft and painless.
  - Senna laxatives if stool softeners are ineffective.
  - Sitting on the toilet for 10 minutes after meals.
  - Non-constipating high-fiber diet.
    - Such foods as popcorn, grains, fruits, and vegetables
  - Limited consumption of milk products.
    - ~10% of children with impactions are drinking great amounts of milk (>32 oz per day).
    - Milk intake can be limited to 16 oz per day in children >1 year.
  - Fluid requirements for these children can be met with fruit juices.
    - Pear, peach, and prune juices have high sorbitol content that can increase stool frequency.
- Non-retentive encopresis.
  - Medications are not needed.
  - Stop all reminders, lectures, or punishments.
  - Give incentives for BMs into the toilet.
  - For soiling, insist on immediate cleanup.
  - Refer treatment failures.

SPECIFIC TREATMENTS

Retentive Encopresis

Disimpaction

- The traditional approach is daily sodium phosphate enema for 2 or 3 days.
  - Excessive doses of phosphate enemas can cause tetany, dehydration, arrhythmias, or death.
  - If the child refuses an enema, administer high-dose mineral oil or polyethylene glycol (MiraLax) orally for 3–4 days.
- These approaches may be combined, starting with mineral oil or polyethylene glycol orally and followed by enemas on day 3.
- Occasionally, enemas must be administered in the office or clinic.
- Rarely, for severe impactions involving the entire colon, a child needs to be hospitalized for the clean out.
  - The usual procedure is to give polyethylene glycol–electrolyte solution by nasogastric tube for 8–24 hours.

Stool Softeners

- First line of therapy for constipation.
- Appropriate for long-term treatment.
- Administered orally.
- Begun as soon as the impaction is eliminated.
- Goal is the passage of 1 or 2 normal-sized BMs per day.
- Continued for 3 months.
  - It takes 3 months for bowel diameter and tone to return to normal.
- Mineral oil.
  - 1–2 mL/kg twice daily.
  - Adolescents: 60 mL/dose (max 236 mL [8 oz]/d).
  - Contraindicated in children who
    - Have gastroesophageal reflux or vomiting
    - Are not yet walking
  - Emulsified derivatives of mineral oil taste better but are more expensive.
- Lactulose
  - 0.5–1.0 mL/kg twice daily
  - Adolescents: 15 mL twice daily (max 89 mL [3 oz]/d)
- Polyethylene glycol (MiraLax)
  - 0.5 g/kg/d
  - Adolescents: 17 g/d

- Milk of magnesia
  - 1–2 mL/kg/dose
  - Adolescents: 30–60 mL

Stimulant Laxatives

- Recommended if stool softeners are not effective.
  - Usually needed for children who deliberately hold back BMs or for those who have developed megarectum and megacolon.
- Treatment failure and recurrence usually are due to under-medicating.
  - Increase dose if child is not having a normal-sized BM daily.
  - Some children temporarily require doses that exceed the standard dose recommended by textbooks and the package insert.
  - Children can be tapered off laxatives successfully, even after 6 months.
  - Continue medications until the child has gone ≥1 month without any soiling.
  - Taper medications gradually over 1–2 months.
- Senokot (senna).
  - <5 years: 1–2 tsp syrup/d
  - ≥5 years: 2–3 tsp syrup/d
  - Adolescents: 1 tbsp/d (max 2.5 tbsp or 8 tablets)
- Fletcher's Castoria.
  - <5 years: 1–2 tsp/d
  - ≥5 years: 2–3 tsp/d
  - Adolescents: 2 tbsp max
- Ex-Lax (senna).
  - >5 years: 1 square/d
  - Adolescents: 2 squares
- Dulcolax, 5-mg tablet.
  - >5 years: 5 mg/d
  - >12 years: 10 mg (2 tablets)
  - Adolescents: 4 tablets max
- Rectal suppositories.
  - Glycerin suppository
    - 1 or 2 suppositories
  - Dulcolax, 10-mg suppository
    - >2 years: 1 suppository
- Enema for disimpaction.
  - Mineral oil enema
    - 1–2 oz/20 lb of body weight/d
    - Adolescents: 4 oz
  - Sodium phosphate enema (Fleet)
    - 1 oz/20 lb of body weight/d
    - Adolescents: 4 oz (max 8 oz)

Oral Disimpaction

- Mineral oil
  - 1 oz per year of age/d
  - Max dose: 8 oz/day
- Polyethylene glycol (MiraLax)
  - 0.5 g/kg 3 times daily
  - Max 25 g, or 1.5 capfuls 3 times daily

Toilet Habits

- The child must sit on the toilet for ≥10 minutes once a day with a timer.
  - The gastrocolic reflex takes effect 20–30 minutes after a meal (especially breakfast).
    - Can be used to advantage.
    - Any treatment that neglects this opportunistic timing will fail.
- Children who have been impacted for many months have no urge to defecate.
  - The defecation urge may not return until the rectum is kept empty for 1–2 weeks.
  - Children should be instructed to flex the hips to open the rectum, to use a footstool for leverage, and to apply some pressure to the abdomen while pushing down.
  - If they have no BM for 24 hours, these children need to sit on the toilet more often and longer each time.
  - Soiling (leakage) requires
    - Sitting on the toilet
    - Cleanup
- Preschoolers and toddlers
  - May refuse to sit on the toilet.
  - May hold back stools when forced to sit on the toilet.
  - The goal is to produce a BM daily.
    - Pediatricians and parents need to lower their expectations.
    - The child can be told that the "poop wants to come out every day and it needs your help."
    - Going in the diaper is fine.
      - The child is not put back in diapers full-time.
      - The diaper is made available when child needs to release a stool.
      - This approach prevents the child from bladder control regression.

Non-retentive Encopresis

- Stool softeners, laxatives, and enemas are not needed.
- For children who simply postpone BMs
  - Admonition "to find a toilet whenever you feel rectal pressure" or "don't make your body wait" usually removes the symptom.

- Stop all reminders, lectures, or punishments.
  - Parents should be reassured that nothing more can be taught to their child.
  - To eliminate the control issue, the parents should be told to let the child decide when the need exists to go to the bathroom.
    - Reminders, inquiries, and lectures are a form of pressure, and pressure does not work.
  - Parents should not threaten punishment.
    - Many young children try to hold back all BMs to avoid punishment for soiling.
    - Parents should be told about the importance of not punishing their child for soiling.
    - Child should be reassured that soiling will no longer incur punishment.
- Give incentives for BMs into the toilet.
  - Immediate positive feedback, such as praise, a hug, or a sticker/stars on a chart.
  - Major incentives may be offered to achieve breakthrough with some children who have never had a BM into a potty chair or toilet.
- Soiling should not be ignored.
  - Immediate cleanup.
  - Parents should help the child change clothes.
  - Changing should be a neutral, timely interaction.
- Most children with non-retentive encopresis are resistant to toilet training.
- If initial behavioral methods are not helpful, more intensive psychological or family interventions are needed.

WHEN TO ADMIT

- Hospitalization is rarely needed for children with constipation.
- For severe impactions involving the entire colon, possible hospitalization for polyethylene glycol-electrolyte solution by nasogastric tube for 8–24 hours.

WHEN TO REFER

- Refer to a mental health professional in the following situations:
  - Non-retentive encopresis unresponsive to pediatric management
  - Child >5 years who refuses to sit on the toilet
  - Child who refuses to take medications
  - Child >8 years with non-retentive encopresis
  - Child with non-retentive encopresis who deliberately passes BMs on family possessions or at school (overt anger)
  - Child who is depressed
  - Severely disturbed parent-child relationship
- Refer to a gastrointestinal subspecialist in the following situations:
  - Repeated impaction
  - Unresponsive constipation
  - Constipation of unknown etiology

FOLLOW-UP

- Follow up ~1 week into treatment.
  - >30% still will be impacted.
  - Some children need enemas in the office.
- If a child still is impacted at the follow-up examination, a more detailed explanation of the disimpaction process is necessary.
- Repeat abdominal examination even if patients report that the child is having normal BMs and no soiling.
  - Children who have an impaction can keep themselves clean temporarily by making a strenuous effort at control and sitting on the toilet several times a day.

COMPLICATIONS

- Secondary emotional problems
  - Shame.
  - Constant fear of exposure.
  - Many children with encopresis are scapegoated at home, teased by peers, and ostracized at school.

PROGNOSIS

- 99% of children who have mainly pain-related impaction are cured by pediatric management.
- ~70% of children who have psychogenic impaction are successfully treated by the pediatrician.
  - The remainder need to work with a mental health professional.
- Non-retentive encopresis.
  - Good results if the problem is recent
  - Poor results if the problem is long-standing (>5 years)
- In mildly resistant children, primary care management can achieve a 90%–95% cure rate.
- Children who have severe resistance need early referral.

PREVENTION

- Backup plans for preventing relapses.
  - Increased dose of stool softener or laxative if >48 hours without a normal-sized BM

- Child is at risk for recurrent impaction if soiling occurs more than twice over a few days.
  - Double dose of laxative, a suppository, or an enema.
    - Merely mentioning an enema sometimes results in the child sitting on the toilet and producing a BM.
  - For older children who are cooperative about sitting on the toilet, sitting there for 10 minutes out of every hour will usually relieve an early impaction.
  - The family should be made to realize that soiling always means that the rectum is full and the impaction is returning.
- Primary care interventions may fail because of
  - Rectal hyposensitivity acquired from prolonged stretching of the rectum.
  - Inability to relax the external anal sphincter caused by voluntary attempts to prevent stool leakage or pain.
  - Both of these conditions usually recede once stool impaction is permanently resolved with more aggressive interventions.

Enterovirus Infections

DEFINITION

- Enteroviruses are members of the Picornaviridae family.
- Share genus with rhinoviruses, polioviruses, and coxsackieviruses.
- Enterovirus serotypes causing more severe disease include polioviruses (EV C), enterovirus 71 (EV A), and enterovirus 68 (EV D).

SIGNS AND SYMPTOMS

- Symptoms range from none to meningoencephalitis or a sepsis-like presentation.
- Infants.
  - ~50% of infants admitted with a fever of unknown origin have an enteroviral infection.
  - Most present with nonspecific fever or meningoencephalitis, but mortality is extremely low.
  - Often present with fever, decreased oral intake, and fussiness.
  - Onset is very rapid, and the mortality rate reaches 24%.
  - Circulatory collapse (shock) or hemorrhage causes most deaths.
  - May present with skin lesions, such as petechiae and purpura, which may resemble purpura fulminans.
  - Myocarditis, an uncommon presentation in infants, has a mortality rate >70%.
  - Rarely, infants present with a sepsis-like picture characterized by hepatic involvement and coagulopathy.
- Older children.
  - Outside of the neonatal period, children often present with fever and nonspecific symptoms.
  - Gingivostomatitis, a febrile illness with vesicles and ulcers in the oropharynx or buccal mucosa, is common.
    - Symptoms may last for a week.
- Hand-foot-and-mouth disease.
  - Combination of oral lesions and vesicular lesions on the hands and feet, specifically the pulp of the fingers and toes.
  - Coxsackievirus A16 is the most common cause in the United States.
- Widespread community outbreaks of hemorrhagic conjunctivitis are associated with enterovirus 70 and coxsackievirus A24.
- Enteroviral meningoencephalitis.
  - Presentations from fever with a mild headache to changes in mental status
- Enterovirus 68.
  - In August 2014, 2 children's hospitals noted increased numbers of patients presenting with respiratory disease.
  - The Centers for Disease Control and Prevention (CDC) identified enterovirus 68 in most of the children.
  - At the time of publication, more than 43 states had confirmed cases of enterovirus 68 infections.
  - Symptoms of enterovirus 68 infection include
    - Mild upper respiratory tract infection with cough, sneezing, and fever to respiratory illness that may trigger severe wheezing and hypoxia.
    - Pulmonary hemorrhage may occur.
  - In September 2014, the CDC issued a health advisory after 9 children in Colorado presented with acute focal limb weakness.
    - Magnetic resonance imaging of the brain and spine demonstrated gray matter changes to the spinal cord.
    - Many tested positive for enterovirus 68.
  - Similar presentations in other parts of the country.
    - A recent article discussed temporal association of enterovirus 68 infection and acute flaccid paralysis.
- Polioviruses.
  - Infection with polioviruses (3 separate enteroviruses) causes a nonspecific illness.
  - These viruses have tropism for neurons, particularly those in the anterior horns of the spinal cord.
  - Acute flaccid paralysis is the most serious complication.
- Enterovirus 71
  - Outbreaks of hand-foot-and-mouth disease in China each year.
  - Linked to neurologic disease in China, with symptoms ranging from meningoencephalitis to acute flaccid paralysis to fatal brain stem encephalitis.
  - Cause of death in patients who have enterovirus brain stem encephalitis is autonomic nervous system dysfunction and acute respiratory distress syndrome.

DIFFERENTIAL DIAGNOSIS

- The differential diagnosis of hemorrhagic conjunctivitis infection should include adenovirus.
- Gingivostomatitis.
  - *Enterovirus* species tend to cause lesions on the tongue and pharynx.
  - Herpes simplex 1 and 2 lesions usually involve the lips and anterior gingiva.
- Echovirus and parechovirus can cause nonspecific febrile illnesses similar to enterovirus.
- Meningoencephalitis in infants and young children can present similarly to herpes simplex infection.
  - Unlike herpesvirus, enterovirus does not typically cause seizures.
- Herpes simplex has high morbidity and mortality and requires prompt treatment with acyclovir, so it is important to consider.
- In young infants, enterovirus infection may present with fever as the only symptom.
  - In the neonate, occult bacteremia, meningitis, and pyelonephritis may also present with fever as the only symptom.

DIAGNOSTIC APPROACH

- Viral diagnostic testing by polymerase chain reaction (PCR)

LABORATORY FINDINGS

- Appropriate specimens for PCR testing include blood, spinal fluid, nasopharyngeal swabs, and rectal swabs (stool).
- Lumbar puncture is necessary to diagnose enteroviral meningoencephalitis.
  - Cerebrospinal fluid testing should include cell count, protein, glucose, and bacterial culture as well as PCR.
  - If contraindicated, enteroviral PCR of serum may help diagnose meningoencephalitis in patients with appropriate clinical symptoms.
- Because infants and young children may shed enterovirus in the stool for weeks, a positive test result from a stool sample is not adequate to diagnose an enterovirus infection.

CLASSIFICATION

- 4 subtypes
  - Enterovirus A (25 viruses)
  - Enterovirus B (61 viruses)
  - Enterovirus C (23 viruses)
  - Enterovirus D (5 viruses)

TREATMENT APPROACH

- When children present for care, the diagnosis of enterovirus infection is not confirmed.
- Treatment is supportive, and antipyretics and intravenous (IV) fluids may be appropriate for some sick children.

SPECIFIC TREATMENTS

- No specific treatment.
  - Infection resolves after the body mounts an effective antibody response.
- Provide supportive care based on symptoms.
  - Infants who are dehydrated might require IV fluids.
  - Patients with severe respiratory distress may require intubation and mechanical ventilation.
- Antivirals.
  - No commercially available agents with activity against enteroviruses.
  - Pleconaril.
    - Effective against some picornaviruses.
    - The medical literature is mixed on whether effective against enteroviruses other than coxsackieviruses.
    - No longer available for clinical or research use.
  - 2 promising antivirals under study include a capsid binder (vapendavir) and a novel protease inhibitor (SG85).
- IV immunoglobulin (IVIG) therapy.
  - May improve survival in patients with enterovirus brain stem encephalitis.
  - No conclusive studies support the use of IVIG for enterovirus infections.
  - However, IVIG therapy is often used to treat immunodeficient patients.
- Enterovirus 68.
  - Treatment is supportive.
  - Patients with respiratory enteroviral disease who have known reactive airway disease or asthma need to take controller medications as prescribed.

WHEN TO ADMIT

- Criteria for referral to a children's hospital include
  - Seizures
  - Encephalitis
  - Acute flaccid paralysis
  - Severe respiratory distress

WHEN TO REFER

- Pediatric subspecialists in critical care medicine, neurology, radiology, and infectious diseases may be helpful in managing hospitalized patients.

COMPLICATIONS

- Poliovirus infections lead to permanent paralysis of muscles innervated by affected neurons.
- Aseptic meningitis may lead to neurologic sequelae, such as speech and language delay.
- Enteroviral infections in neonates may be fatal.

PROGNOSIS

- There is no evidence that enteroviral meningoencephalitis has long-term effects on central nervous system development later in life.
- Herpangina and mild febrile illnesses resolve with time.
- A sepsis-like presentation with hepatitis and coagulopathy in neonates is uncommon, but the mortality rate is quite high.
- Encephalitis typically resolves without sequelae.
- Acute flaccid paralysis may be permanent.

PREVENTION

- Vaccination
  - Although oral and inactivated poliovirus vaccines eradicated disease from all areas with high vaccination rates, there is no current vaccine effective against other enteroviruses.
  - Inactivated viral particle vaccine studies are underway.
  - The major challenge to development is that some subtypes, such as enterovirus 71, have multiple serotypes.
  - Viruses of varying serotypes can recombine their RNA to create new proteins that may confer vaccine resistance.
- Infection control
  - Basic infection control practices prevent most cases.
  - The CDC recommends hand hygiene with soap and water or waterless alcohol rub.
  - Respiratory transmission means that cough etiquette and avoiding nasal secretions may be beneficial.
    - Health care workers should institute contact precautions (gown and gloves).
    - When caring for infants, consider adding a surgical mask (droplet precautions) as well.

DEFINITION

- Urinary incontinence occurring when a child
  - Is at least 5 years old *and*
  - Urinates in bed or on clothes
    - — At least twice per week
    - — For at least 3 consecutive months
- Variations
  - Daytime incontinence (The term "diurnal" has been dropped.)
  - Nocturnal
    - — The term is often added to enuresis for more clarity.
    - — Daytime and nighttime wetting is referred to as *incontinence* and *enuresis* (or *nocturnal enuresis*).
    - — Monosymptomatic nocturnal enuresis (MNE): no daytime symptoms to suggest lower urinary tract disorders.
    - — Polysymptomatic: associated with additional symptoms.
      - Urgency
      - Frequency
      - Daytime incontinence
      - Hesitancy
      - Straining
      - A weak stream
      - Intermittence
      - Holding maneuvers
      - Feeling of incomplete emptying
      - Post-micturition dribbling
      - Genital or lower tract pain
  - Primary
    - — Children who have never had a period of sustained dryness
  - Secondary
    - — Children who have been dry in the past
      - ≥6 months with nocturnal enuresis
      - ≥3 months with daytime incontinence

SIGNS AND SYMPTOMS

History

- Determine nocturnal or daytime incontinence.
  - Does the wetting occur during the day, the night, or both?
  - How often does wetting occur and at what times?
  - How often does the child void during the day and during the night?
- Determine primary or secondary enuresis.
  - What age did the wetting start?
  - Has the child ever been dry? If so, for how long?
  - Has the child had any dry spells?
    - — How long did dry spells last?
  - What has been done about the symptom before this evaluation?
- Social situation.
  - How does the family handle wet nights?
    - — Does the child wear training pants or is a plastic sheet used?
    - — Who is responsible for laundering sheets and clothing?
    - — Do siblings tease the child?
    - — Is the child punished for wetting?
  - Any recent traumatic events or changes in social situation at home or in school?
- Fluid intake before bedtime.
  - How much and how often does the child drink in the daytime?
  - How much and when does the child drink after supper?
- Sleep habits.
  - Is the child difficult to wake from sleep?
  - Are there any signs of obstructive sleep apnea (eg, mouth breathing, snoring, restless sleep)?
- Daytime symptoms.
  - Urinary frequency (normal = 4–7 times per day).
  - Urgency.
  - Dysuria.
  - Dribbling between voids.
  - Straining with voids.
  - Child is always wet.
  - Constipation.
- Medical history, including a thorough perinatal history.
  - Has the child had normal development?
  - Spina bifida or meningomyelocele.
  - Delayed developmental motor milestones.
  - Spinal trauma.
  - Psychological issues.
    - — Attention-deficit/hyperactivity disorder (ADHD)
    - — Depression
    - — Conduct disorder
    - — Feelings about the enuresis
    - — Motivation for doing something about it
  - History of enuresis in one or both parents.
  - History of polydipsia and polyuria.
  - History of recent weight loss.

Physical Examination

- Physical examination is often normal.
- Examination should be thorough with focus on signs that may indicate any of the causes of enuresis.
  - Abnormal vital signs and growth parameters may indicate chronic disease.

- A thorough oropharyngeal examination may reveal the presence of tonsillar enlargement, especially in children with suspected obstructive sleep apnea.
- Complete neurologic examination.
  - Gait
  - Muscle tone and strength
  - Deep-tendon reflexes
  - Sensory abnormalities
- Spinal examination may reveal subtle signs of spinal dysraphism.
  - Dimples.
  - Hair tuft.
  - Skin discoloration.
  - Let the child grasp a pencil with his toes.
    - If he is able to do so, S1, S2, and S3 are intact.
    - Ask him to do it bilaterally.
- Abdominal examination.
  - Distended bladder
  - Constipation
- Rectal examination.
  - Fecal impaction.
  - Decreased rectal tone.
  - Observing a child void may reveal important clues to the presence of urethral obstruction, such as a weak urine stream and straining during micturition.
- Flank examination.
  - Lower abdominal tenderness may indicate urinary tract infection.
- Genitourinary examination.
  - Rash
  - Adhesions
  - Trauma
  - Foreign body
  - Vulvitis
  - Vaginitis

DIFFERENTIAL DIAGNOSIS

- Focuses on excluding underlying disorders
  - Urinary tract infection
  - Renal masses or renal diseases
  - Neurologic disorders
    - Neurogenic bladder
    - Detrusor instability
    - Spinal cord conditions
  - Structural genitourinary tract defects
    - Ectopic ureter
    - Posterior urethral valves
    - Urethral stricture
    - Vesicovaginal reflux
  - Constipation
  - Endocrine disorders
    - Diabetes mellitus
    - Diabetes insipidus
  - Hypercalciuria
  - Sickle cell disease
  - Drugs
    - Caffeine
    - Methylxanthines
  - Obstructive sleep apnea
  - Psychosocial stressors, including child abuse, parental divorce or separation, and death in the family

DIAGNOSTIC APPROACH

- Diagnosis depends on a thorough history and physical examination.
- Imaging is indicated
  - In the presence of daytime symptoms
  - If initial laboratory evaluation and physical examination are abnormal

LABORATORY FINDINGS

- Urinalysis
  - Useful in MNE
  - Renal pathologic abnormality
    - Proteinuria
    - Hematuria
    - Red blood cell casts
  - Diabetes mellitus
    - Glucosuria
  - Diabetes insipidus, psychogenic polydipsia
    - Low specific gravity.
    - The presence of white blood cells and bacteria may suggest a urinary tract infection.
- Urine culture
  - Diagnostic for urinary tract infection

IMAGING

- Ultrasound
  - Prevoid and postvoid renal and bladder
- Voiding cystourethrogram, urodynamic studies if ultrasound result is abnormal
- Spine magnetic resonance imaging
  - To rule out possible spinal dysraphism

TREATMENT APPROACH

- Treat any underlying cause(s).
- Consider treatment of MNE in children 6–8 years of age.
  - Conservative measures.
  - Careful/detailed explanation to parents and child.
  - Alarm therapy is most effective.
- Pharmacotherapy depends on underlying cause.

SPECIFIC TREATMENTS

General

- Treat any underlying organic causes.
- If daytime and nighttime symptoms are present, daytime symptoms should be treated first.
- Good voiding hygiene and habits should be reinforced.
- Primary and secondary nocturnal enuresis are treated similarly.
- In children <8 years.
  - Conservative measures
    - Training pants
    - Plastic-lined bedsheets
- MNE.
  - Treatment should be considered in a child 6–8 years of age.
    - Provide careful and detailed explanation of the condition to parents and child in language that is easily understood.
    - Expect relapses.
  - The combination of a motivated child and a cooperative family is the best predictor of a positive outcome.
  - Alarm therapy should be considered in most patients ≥8 years.

Nonpharmacologic Therapy

- Conservative measures to minimize nocturnal polyuria
  - Decrease fluid intake several hours before bedtime.
  - Void before bed to minimize nocturnal bladder volume.
  - Consider awakening the child to urinate before the parents go to bed.
  - Encourage the child to void often during the day and take the time to empty the bladder completely.
- Charts for positive reinforcement
  - Children fill out a chart depicting wet and dry nights symbolically, such as stars or the sun for dry nights and a cloud for wet nights.
- Enuresis alarm therapy
  - In some families, alarms may increase parental annoyance and place the child at risk for physical or emotional abuse.
  - Many children will not initially awaken with the alarm and need a parent to assist in awakening.
  - The alarm should be used for 2–3 months or until the child is dry for 14 consecutive nights, whichever comes first.
  - Although response rate is not as rapid, alarm therapy is more effective than pharmacologic therapy in the treatment of enuresis.
  - Response rate to the alarm is high in families who continue treatment for a sufficient period, with relatively low relapse rates.
  - Relapses do not preclude future success.
- Dry bed training
  - Effective, comprehensive program combining
    - Enuresis alarms
    - Positive practices
    - Waking routines
    - Personal cleanliness routine after enuresis
    - Bladder training

Pharmacotherapy

- Desmopressin (DDAVP)
  - First-line treatment often together with alarm therapy for MNE.
  - Efficacy.
    - Dose-dependent effect.
    - Usual dose is 0.2 mg up to 0.6 mg orally at bedtime.
    - Produces improvement in 2–3 months.
  - Side effects.
    - Nausea
    - Vomiting
    - Abdominal pain
    - Headache
    - Facial flushing
    - Elevated blood pressure
    - Chest pain
    - Tachycardia
    - Hyponatremia from water intoxication
  - If treatment is successful, a 1-week interruption every 3 months is recommended to see if enuresis has resolved.
  - Some patients who do not respond to the usual dose of desmopressin may respond when the dose is doubled.
  - If no response to medication alone, alarm therapy should be considered.
  - Relapse is common with desmopressin use.
- Oxybutynin
  - Useful in treating daytime enuresis caused by detrusor overactivity
    - May be of benefit to enuretic children with restricted bladder capacity caused by bladder overactivity

- Efficacy
  - — Ineffective as a single agent for primary enuresis.
  - — Combined therapy with oxybutynin and desmopressin produces more rapid results for MNE than single therapy with either desmopressin or imipramine.
- Also used to treat
  - — Urge incontinence
  - — Hinman syndrome
  - — Neurogenic bladder
- Side effects
  - — Nausea
  - — Vomiting
  - — Abdominal pain
  - — Diarrhea
  - — Constipation
  - — Urinary retention
  - — Dry mucous membranes
  - — Blurred vision

■ Imipramine/tricyclic antidepressants
- Last-line treatment.
- Efficacy.
  - — Minimal effectiveness in treatment of MNE.
  - — Relapse is common.
- The anti-enuretic dose is 25–50 mg at bedtime, with a larger dose given in children >9 years.
- Side effects.
  - — Potential for lethal effects in the setting of accidental or intentional overdose
    - ■ Clinicians must use caution in prescribing these agents.
    - ■ Families must be aware of dangerous potential of overdose and need for safe storage and supervision.
  - — Nausea
  - — Vomiting
  - — Constipation
  - — Blurred vision
  - — Urinary retention
  - — Cardiac arrhythmias
  - — Hypotension

Other Therapies

■ Behavioral modifications, such as
- Changes in toileting habits.
- Waking after several hours of sleep to void.
- A recent prospective, randomized study comparing the use of desmopressin and intensive behavior modification showed significant reductions in primary MNE, with no significant difference between the 2 groups.

WHEN TO REFER

■ Abnormal urinalysis findings suggestive of a metabolic disorder
■ Concerns of neurologic bladder dysfunction
■ Failure to respond to appropriate therapy
■ Presence of any structural urinary tract abnormalities on imaging studies
■ History of
- Recurrent urinary tract infections
- Significant constipation and encopresis
- Findings suggestive of obstructive sleep apnea

■ Significant behavioral or emotional problems
■ Significant parent-child conflict or parental difficulties with coping with child's enuresis
■ ADHD or learning problems

PROGNOSIS

■ Nocturnal enuresis
- Annual spontaneous resolution rate is ~15%.
- With alarm therapy
  - — Long-term cure rate of MNE with alarm therapy
    - ■ 25% by 2 months
    - ■ 50% by 3 months
    - ■ 90% by 6 months
  - — 47% remain dry long term after alarm therapy is stopped.

DEFINITION

- Acute bleeding from the nostril, nasal cavity, or nasopharynx
  - Relatively common and usually self-limited occurrence in childhood
  - Can be extremely distressing to children and parents when profuse or recurrent
  - Can, at times, be a sign of a more serious condition
- Anterior epistaxis
  - Accounts for >90% of epistaxis in children.
  - Almost all the blood exits anteriorly through the nares.
  - Much easier to visualize and control than posterior bleeding.
- Posterior epistaxis
  - Most of the blood flows into the nasopharynx and mouth, making the degree of bleeding difficult to assess.
  - Bleeding is generally much more profuse than anterior bleeding.
  - More likely than anterior bleeding to lead to hemodynamic instability.

PHYSICAL EXAMINATION

- Blood pressure and pulse if the history suggests significant acute or chronic blood loss.
- Careful examination of the nose.
  - Attempt to identify the source of any active bleeding.
  - Note any discharge, obstructing mass, or foreign body.
- The neck should be examined for the presence of a mass.
- The skin should be checked for petechiae or unusual location or number of ecchymoses.
- If the child is ill, perform a full examination, including a search for lymphadenopathy and hepatosplenomegaly.

DIFFERENTIAL DIAGNOSIS

Local Causes

- >1 factor often plays a role in the bleeding.
  - Trauma from nose picking or rubbing
    - — Accounts for most cases in children, particularly in association with inflammation from infection or allergy
  - Blunt external trauma
    - — Generally acute and self-limiting
    - — Should prompt evaluation for fractures of the facial bones and an anterior septal hematoma
    - — Could result from abuse in very young children
  - Trauma from a foreign body
    - — Occasional cause in toddlers
    - — Often results in unilateral bleeding accompanied by foul-smelling or bloody discharge
  - Upper respiratory infection and allergic rhinitis
    - — Resultant rhinorrhea leads to digital manipulation or forceful sneezing and nose blowing.
    - — Vascular congestion and mucosal irritation promote easy injury to the blood vessels of the anterior septum.
    - — Association in children of positive allergy skin tests and recurrent epistaxis.
  - Low environmental humidity, especially in winter months
  - Deviated nasal septum
    - — Can contribute to recurrent epistaxis by causing a change in normal airflow, leading to mucosal drying and irritation
  - Colonization with *Staphylococcus aureus* leading to chronic inflammation and neovascularization
  - Intranasal drugs (eg, steroids, cocaine)
  - Neoplasms (benign or malignant)
    - — Uncommon in children but should be considered in certain circumstances.
    - — Polyps in children are usually associated with cystic fibrosis.
    - — Juvenile nasopharyngeal angiofibroma.
      - Benign vascular tumor originating in the lateral nasopharynx.
      - Occurs only in male adolescents because of its hormonal sensitivity.
      - Recurrent epistaxis is the most frequent presenting symptom.
      - Unilateral progressive obstruction or discharge are clues to the diagnosis.
    - — Rhabdomyosarcoma of the nasal cavity or nasopharynx.
      - A rare malignant cause of severe episodic epistaxis
      - May be associated with signs of eustachian tube dysfunction, such as unilateral middle ear effusion
    - — Nasal hemangioma.
      - Rare
      - Should be considered in infants
    - — Nasopharyngeal carcinoma.
      - Extremely uncommon but serious disease in children.
      - Epistaxis is the presenting symptom in ~50% of children.
      - Nearly always accompanied by a neck mass or neck pain.

Systemic Causes

- Should be considered whenever nosebleeds are recurrent or persistent in the absence of any obvious local cause
- Epistaxis scoring system (**Table 1**)
  - Frequency, duration, amount, age at onset, and bilateral epistaxis have been used to determine which patients should be evaluated for an underlying bleeding disorder.
- Hematologic disorders (congenital or acquired)
  - Primary coagulation defects
    - May result in persistent and long-standing epistaxis.
    - Positive family history is often present.
    - Up to one-third of children with isolated recurrent epistaxis have a diagnosable coagulopathy.
    - von Willebrand disease (vWD).
      - The most commonly identified inherited coagulopathy.
      - 60% of patients with vWD have recurrent epistaxis.
      - Other mucosal bleeding (eg, menorrhagia, bleeding after surgery or dental extraction) is also common in older children and adolescents.
      - Epistaxis of long duration, lacking seasonal correlation and requiring medical intervention, has been significantly associated with vWD.
    - Hemophilia (deficiency factor VII, VIII, IX, or XI).
      - Less common than vWD
      - In mild cases, may cause isolated epistaxis
  - Thrombocytopenia
    - Almost always accompanied by petechiae or ecchymoses
    - Immune thrombocytopenia purpura
      - Most common cause of isolated thrombocytopenia in otherwise healthy children.
      - Presents as acute mucosal hemorrhage, often epistaxis, in ~30% of patients.
      - Bleeding is rarely severe.
    - Can be an adverse reaction to a variety of medications, including anticonvulsants, such as carbamazepine and chemotherapeutic agents
  - Disorders of platelet function
    - Platelet dysfunction from aspirin or nonsteroidal anti-inflammatory drugs can predispose to epistaxis.
    - Bernard-Soulier syndrome is a disorder of platelet aggregation occasionally diagnosed in children with isolated epistaxis.
  - Leukemia
    - Epistaxis is rarely the first symptom.
    - Should be considered in an ill-appearing child with epistaxis, especially with fever, pallor, lymphadenopathy, or hepatosplenomegaly.
  - Acquired coagulopathies
    - Unlike adults, rare cause of epistaxis in children.
    - Include various liver diseases (eg, chronic active hepatitis) with consequent depletion of clotting factors.
    - An acquired form of vWD has been described in children receiving valproic acid.
- Vascular abnormalities
  - Hereditary hemorrhagic telangiectasia (Osler-Weber-Rendu disease)
    - Autosomal-dominant disorder of the blood vessel walls.
    - Characterized by the progressive development of cutaneous and mucosal telangiectasias.
    - >90% of affected patients have recurrent and progressively worsening epistaxis.
    - Present at a mean age of 12 years.
    - Gastrointestinal bleeding and pulmonary arteriovenous malformations occasionally also occur in childhood.
- Primary isolated hypertension
  - Has not been clearly associated with epistaxis in children, except in the context of renal failure

LABORATORY EVALUATION

- The need for and extent of laboratory testing should be guided by history and physical examination.
- Frequent and prolonged episodes may warrant ruling out anemia caused by blood loss.
- Complete blood cell count.
  - Always indicated in the presence of petechiae or unusual ecchymoses to rule out thrombocytopenia
  - Will help rule out leukemia in an ill child with pallor, fever, lymphadenopathy, or hepatosplenomegaly

Table 1. Epistaxis Scoring System

Component	Score[a]
Frequency	
5–15/y	0
16–25/y	1
>25/y	2
Duration	
<5 min	0
5–10 min	1
>10 min	2
Amount[b]	
<15 mL	0
15–30 mL	1
>30 mL	2
Epistaxis history and age[c]	
33%	0
33%–67%	1
>67%	2
Site	
Unilateral	0
Bilateral	2

[a] Mild, 0–6; severe, 7–10.
[b] Estimation of average blood loss per episode, based on fractions or multiples of teaspoons, tablespoons, or cups.
[c] Proportion of the child's life that nosebleeds had been recurrent (>5/y).

From Katsanis E, Luke KH, Hsu E, Li M, Lillicrap D. Prevalence and significance of mild bleeding disorders in children with recurrent epistaxis. *J Pediatr.* 1988;113(1):73–76. Copyright © 1988, Elsevier, with permission.

- Prothrombin time and partial thromboplastin time.
  - Useful as initial screening tests for vWD
    - Results may be within reference range in some patients with vWD.
    - Further evaluation with von Willebrand factor studies may be necessary.

IMAGING

- Rarely indicated.
- Plain radiographs can rule out associated fracture of the facial bones in the setting of blunt trauma.
- Computed tomography should be considered if a mass is thought to be present.

DIAGNOSTIC PROCEDURES

- Identifying the source of posterior bleeding must be done by an otolaryngologist using a flexible fiberoptic nasopharyngoscope.
  - Sedation may be required for younger patients.
  - Endoscopic visualization may also reveal such causes as foreign bodies, tumors, or sinusitis.
  - In older, more cooperative patients, a rigid endoscope may be used.
- Cauterization of a posterior bleeding site can be performed under general anesthesia.
  - Posterior packing can be done with gauze or even urinary catheter balloons.
    - Other types of packing include premade nasal tampons or balloons.

TREATMENT APPROACH

- Management can be divided into 3 general phases.
  - Initial first aid measures
    - Often performed at home.
    - Should also be the first line of treatment on presentation to the physician.
    - Parents should be educated about the home management of an acute nosebleed.
  - Acute management of persistent bleeding
    - May be initiated by a pediatrician in an office or emergency department
    - May have to be continued by an otolaryngologist if initial measures are unsuccessful
    - May involve medical or surgical intervention
  - Long-term preventive treatment of recurrent epistaxis
    - Including evaluation and treatment of underlying causes
- Once acute episode of epistaxis has resolved
  - Look for predisposing factors or causes.
  - Implement respective preventive strategies or specific management.
  - If allergic rhinitis is a factor
    - Appropriate testing and medical management are indicated.
    - Treat with inhaled topical nasal steroids.
  - For sinusitis, oral antibiotics are prescribed.
- Management of recurrent nosebleeds
  - Common challenge for physicians.
  - No consensus on the frequency or severity of episodes that warrant medical intervention.
  - Common interventions for less severe cases include
    - Cautery with silver nitrate
    - Antibiotic nasal creams
      - Cautery combined with antibiotic cream has been shown to be more effective than cream alone.
    - Nasal saline spray
    - Coating of the interior nose with ointments, such as petroleum jelly
  - Topical vasoconstriction.
    - Oxymetazoline 0.05% (Afrin)
    - Phenylephrine 0.25% (Neo-Synephrine)
    - Epinephrine 1:1,000
    - Cocaine hydrochloride solution 3%–5%
  - Topical anesthesia.
    - Lidocaine 4%
    - Cocaine hydrochloride solution 3%–5%
    - Ethyl chloride
  - More invasive measures rarely indicated in children.
    - Arterial embolization for refractory bleeding
    - Arterial ligation for recurrent epistaxis
  - A recent Cochrane review of the literature on interventions for recurrent idiopathic epistaxis in children (<16 years) exposed the lack of evidence for current treatments.
    - No single treatment (neomycin-chlorhexidine antiseptic cream, silver nitrate cautery, petroleum jelly) was found to be superior to another or to no treatment.
    - No serious adverse effects were experienced; silver nitrate cauterization caused pain in children despite topical anesthesia.
    - High-quality studies are needed to ascertain which, if any, of these remedies are most effective.

SPECIFIC TREATMENT

First Aid Measures

Direct Pressure

- Many health care professionals and patients are unaware of the proper spot for applying direct pressure to stop a nosebleed.
  - Vast majority of bleeding episodes originate anteriorly, in the Kiesselbach area.
  - Apply pressure to the alar nasi using the first and second fingers.
  - Pressure should be held by pinching the nostrils without interruption for 5–10 minutes.
  - The child should sit up with the head bent forward slightly.
    - Minimizes blood dripping posteriorly and being swallowed, which can cause nausea and hematemesis
  - Some clinicians suggest placement of ice packs on the forehead, bridge of the nose, nape of the neck, or upper lip to promote vasoconstriction.
    - Only theory supports this practice.

First Aid in the Health Care Setting

- Initial treatment measures should occur simultaneously with assessment and history taking.
- Basic equipment should be readied.
  - Examination
    - Flashlight *or*
    - Otoscope with speculum *or*
    - Headlight and nasal speculum suction
  - Topical anesthesia
    - 4% lidocaine *or*
    - 3%–5% ethyl chloride solution

- Hemostasis
  - Silver nitrate sticks
  - Petroleum jelly strip gauze
  - Oxycellulose sponges *or*
  - Gelatin sponges *or*
  - Nasal tampons/expandable nasal pack
- Additional items
  - Antibiotic ointment or cream
  - Cotton pledgets, gauze
  - Gown, gloves, mask

- Most anterior nosebleeds in children will stop after basic first aid.
- If bleeding persists, additional measures are available.
  - As in any acute situation, an initial CAB (**c**irculation, **a**irway, **b**reathing) assessment should be made.
  - Evaluation for major hemorrhage includes evaluating for tachycardia, hypotension, and orthostasis.
- Attempt to locate the source of bleeding.
  - Bleeding has often stopped by the time medical attention is sought.
  - The child should be asked to blow out all clots.
    - If this is not possible, blood in the nose can be suctioned out.
  - To try to visualize the source of bleeding, use
    - A flashlight, while applying gentle upward pressure to the nasal tip *or*
    - An otoscope with speculum *or*
    - A headlight and nasal speculum
  - Inspect the anterior septum first.
  - Anterior bleeding on the septum, or lateral wall, should be evident by
    - Active bleeding
    - Clots
    - Crusts
    - Ulcerations
    - Prominent blood vessels
  - If an anterior source is not found and posterior bleeding is suspected, an otolaryngologist should be consulted immediately.
    - Posterior bleeding is usually profuse and difficult to stop.

Topical Vasoconstrictors

- Use if anterior bleeding has not ceased with application of pressure alone.
- Oxymetazoline 0.05%, phenylephrine 0.25%, epinephrine (1:1,000), or cocaine hydrochloride solution 3%–5% can be applied with a cotton pledget to
  - Shrink the nasal mucosa to improve visualization.
  - Possibly slow down or stop the bleeding.
- Pressure, again by pinching, should be applied for another 5–10 minutes.

Chemical Cauterization

- Next step to attempt to stop persistent hemorrhage
  - Local anesthesia should be administered with a cotton pledget for 5 minutes to reduce the discomfort of cauterization.
  - Insert and open a nasal speculum.
  - Using adequate lighting, apply silver nitrate on applicator sticks to the bleeding point.
    - Can be rolled over the site for 5 to 10 seconds.
    - May have to be repeated 2 to 3 times to achieve hemostasis.
    - Silver nitrate does not work well in pools of blood; therefore, suction may be necessary to keep the area dry.
    - A gray eschar will form at the cautery site.
    - Remove excess silver nitrate with cotton or gauze to minimize dispersion by nasal secretions and resulting injury to intact mucosa.
  - Caution should be used to avoid cauterizing too large or too deep an area or both sides of the septum.
    - Can lead to septal perforation
  - After cauterization
    - Prescribe antibiotic cream or ointment to apply to the area twice a day for 5 days to prevent crusting and infection.
    - Hydration with saline or ointment should continue until healing is complete (~1–3 weeks).
    - Nasal trauma and forceful nose blowing should be avoided.
  - Otolaryngologists may use electrocautery as another hemostatic measure.
    - Cannot be performed with topical anesthesia alone

Nasal Packing

- Nasal packing may be required if anterior bleeding persists despite direct pressure or nasal cautery.
  - Packing is uncomfortable, requires subsequent removal (usually after 2–3 days), and can cause additional mucosal injury.
  - All types of packing and sponges should be impregnated or coated with antibiotic ointment to prevent toxic shock syndrome, a reported complication of anterior and posterior nasal packing.

- Petroleum jelly gauze
  - Layered into the anterior nose
  - Provides a tight pack
- Oxycellulose or gelatin sponges
  - Absorbable and do not require later extraction.
  - Do not apply a great deal of pressure to the bleeding site but are usually adequate for most nosebleeds.
- Commercially available nasal tampons made of a dehydrated polyvinyl polymer sponge
  - Are inserted dry and then expand with blood or added saline partially to fill the nasal cavity.
  - Come in many sizes and can be cut to fit a child's nasal cavity.
  - Must be removed, usually after 3–5 days, and have a tendency to adhere to the nasal lining.
- Prophylactic antibiotics
  - No clear evidence exists to prove that they reduce the incidence of serious infection.
  - Studies have shown that they reduce gram-negative bacterial growth.
  - Common practice is to prescribe them for any patient with nasal packing.
  - May also help prevent sinusitis that can result from stasis of nasal secretions when packing is in place.

WHEN TO REFER

- Ear, nose, and throat
  - Urgent referral
    - Profuse, uncontrollable bleeding
    - Inability to locate source of bleeding
    - Posterior bleeding
    - Assistance with anterior packing
    - Recurrence of bleeding after initial emergency department measures
  - Nonurgent referral
    - Removal of anterior packing
    - Recurrent epistaxis
    - Evaluation for structural lesions (ie, granulomas, tumors, polyps)
    - Treatment of specific lesions
- Hematology
  - Abnormal coagulation laboratory profile
  - Severe, persistent, or recurrent bleeding
  - Bleeding from >1 site, based on history or physical examination
  - Bleeding that required blood transfusion or iron therapy
  - Family history of coagulopathy

WHEN TO ADMIT

- Airway compromise or hemodynamic instability on presentation

FOLLOW-UP

- Posterior nasal packing in place
  - Must be monitored in an intensive care unit for airway obstruction and respiratory compromise

PREVENTION

- In a dry environment, increased moisture
  - Helps prevent the accumulation of crusts, which are often the impetus for nose picking
  - Keeps scabs soft, allowing them to stay in place longer, promoting healing of underlying mucosal injury
    - Physiologic (normal) saline nasal spray to humidify the nasal cavity, used 4–5 times a day
    - Home humidifier
- Local trauma should be minimized.
  - Discourage nose picking, forceful rubbing, or blowing of the nose.
  - Trim fingernails.

Failure to Thrive: Pediatric Undernutrition 339

DEFINITION

- Abnormal pattern of weight gain in children <2 years.
  - Weight consistently <80% of the median for age
  - Weight on >1 occasion falling below the third percentile for age
  - Weight that has fallen across 2 major percentiles on growth charts
    - World Health Organization growth charts recommended for children between birth and 24 months of age
    - National Center for Health Statistics growth charts recommended for children 24–59 months of age
- US Social Security Administration definition.
  - A drop in weight to below the third percentile
  - In children <2 years, drop in weight to <75% of the median weight for height or weight for age
- When acute malnutrition results in decreased weight for age, the condition is referred to as *wasting*.
- If caloric deprivation is prolonged, it will eventually affect the child's linear growth as well, at which point the child is said to be *stunted*.
- Abnormalities in linear growth not accompanied by wasting (ie, the child who has short stature alone) are not failure to thrive.
- Recent scholarship has found the term *failure to thrive* unenlightening and pejorative and replaced it with
  - Pediatric undernutrition (Bright Futures)
  - Weight faltering (British literature)

HISTORY

- Prompt evaluation of infants and children who do not gain weight as expected is important.
- The physician should begin by asking the parent or parents, guardian or guardians, or principal caregiver or caregivers how they think the baby is doing and what they believe the problem to be.
- Every evaluation of an infant or child who is not gaining weight must begin with a thorough history.
  - Gestational age at birth
  - Any unusual complications of labor and delivery
  - Presence of malformations or other obvious deformities
- Knowledge of a parent's frame of mind may propel further evaluation toward or away from difficulty in parent-child interaction, including child neglect.
- Feeding history.
  - Consider observing a feeding while taking an infant's history.
  - During the first year of life, maternal and infant feeding behaviors may significantly affect rate of weight gain.
  - Is the baby bottle-fed or breastfed?
    - How often does the infant breastfeed, and for how long?
    - Does the mother feel as though the infant is sucking well?
    - Does the infant appear sated after feeding?
    - If bottle-fed, how is the formula prepared and by whom?
    - What is the infant's sleep pattern?
    - How many ounces will the infant take in a 24-hour period?
    - Does the infant wet 6–8 diapers a day?
  - For older children, when were solids introduced?
  - Does the parent find the child to be a picky eater or difficult to interest in food?
  - Does the child drink excessive amounts of juice during the day, substituting for more calorically rich nutrients?
  - What are mealtimes like at home?
  - Where does the child eat, and with whom?
  - Are distractions, such as television, video games, or smartphones, present during meals?
  - Is food being used for discipline or in battles over control?
  - A 24-hour dietary recall of a typical day often can help quantify the caloric intake of the patient.
    - If this information proves difficult to elicit, the parents can be sent home with a nutritional diary to fill out prospectively and bring in at the next visit.
  - A home visit provides an opportunity to observe the family interaction around feeding in the context in which it normally occurs.
- Vomiting or spitting up.
  - Frequency.
  - Volume.
  - Presence of blood or bile in the emesis.
  - Gastric outlet obstructions (pyloric stenosis, antral web) often result in the generation of significant propulsive forces leading to projectile vomiting.
  - Gastroesophageal reflux often results in less dramatic patterns of regurgitation.

- An obstruction distal to the ligament of Treitz will generally produce bilious vomiting.
  - In infants, this symptom may indicate the presence of a malrotation and midgut volvulus.
- Pattern and frequency of stooling.
  - Liquid stools may indicate a small-bowel pathologic condition.
  - Bulky, foul-smelling stools may result from fat malabsorption.
  - Mucus or blood in the stools may indicate an inflammatory condition.
- Additional information should be obtained about the medical history, beginning with the parents' attitudes about their decision to have a baby and what their experience with the pregnancy was like.
  - Did the mother gain a reasonable amount of weight?
  - Did she experience any illnesses during her pregnancy?
    - Hypertension or preeclampsia will result in a neonate who is small for gestational age.
    - Gestational diabetes may produce a neonate with macrosomia who fails to gain weight because of postnatal cardiac complications.
  - Ask about specific toxic exposures in utero.
    - Tobacco use may result in a small neonate, but he or she rapidly catches up in weight with peers.
    - Marijuana and alcohol use exert an influence on growth that may be sustained throughout childhood.
- Family history.
  - Growth patterns of siblings.
  - Occurrence of fetal loss or neonate/infant deaths.
  - Presence in the family of immune deficiencies, neurologic disorders, or metabolic derangements.
  - Any unexplained growth deficiencies in close relatives.
  - Recent comprehensive longitudinal studies from England emphasize the extent to which mean parental height and parity overwhelm the influence of traditional markers of socioeconomic deprivation on infant weight gain, such as parental education or occupational status.
- Social history.
  - Availability of social supports for the parents
  - Economic or legal circumstances that threaten the stability of the family
  - Nature of the relationship between the parents
  - Presence of affective disorders, particularly depression, in either parent
  - Substance use in the home
  - Recent disruptive events in the family's life
  - Involvement of child protective services
- Finally, look for unrealistic expectations for feeding patterns, dietary fads, or infant behavior.

PHYSICAL EXAMINATION

- Initial examination begins with observation of how the child relates to the parent or parents and the examiner.
  - Does the child appear listless, easily distractible, or irritable?
  - Can the child be engaged to make eye contact or to play with an age-appropriate toy?
- Repeated anthropometric measurements over time constitute the most important component of the physical evaluation of children who are not gaining weight.
  - Assemble all data available from previous anthropometric measurements of the patient, including weight, height, and head circumference.
  - Preterm newborns must have their measurements corrected for gestational age.
    - Until 18 months of age for head circumference
    - Until 24 months of age for weight
    - Until 40 months of age for height
- The child should be completely undressed, and notations should be made of
  - Any evidence of wasting
  - Presence and distribution of normal subcutaneous body fat
  - Muscle mass and tone
  - Any dysmorphic features
- Particular attention should be paid to organ systems that may reflect evidence of malnutrition.
  - Mucous membranes, hair, nails, and skin
    - Abnormalities may indicate vitamin, protein, fat, and micronutrient deficiencies.
  - Head, eyes, ears, nose, and throat
    - Mouth may reveal extensive dental disease or abscess.
    - Open fontanels may indicate hypothyroidism.
    - Craniotabes are seen in nutritional rickets.
    - Blurred disk margins of increased intracranial pressure are seen in chronic emesis.
    - Submucosal cleft of the hard palate is seen in infants who feed poorly.
- Thyroid.
  - Palpated gently
  - Auscultated for evidence of hyperthyroidism

- Lungs and heart.
  - Observation, palpation, and, particularly, auscultation may reveal wheezing, rales, or heart murmurs suggestive of the presence of chronic conditions.
  - These conditions often result in energy expenditures that can outstrip the supply of nutrients available to an infant.
  - Examine the digits for clubbing in older children.
- Abdominal examination.
  - To rule out organomegaly associated with tumor, infection, or storage disease.
  - Intestinal distention can be associated with carbohydrate malabsorption.
- Neurologic examination, being watchful for
  - Disorders of mentation
  - Cranial nerve abnormalities
  - Generalized weakness
  - Spasticity

DIFFERENTIAL DIAGNOSIS

- Conditions that increase energy needs
  - Chronic heart disease (congenital or acquired)
  - Chronic lung disease (bronchopulmonary dysplasia, cystic fibrosis, pulmonary lymphangiectasis)
  - Chronic anemia (hemoglobinopathies, enzyme deficiencies, membrane abnormalities)
  - Chronic infection (urinary tract infections, respiratory infections, tuberculosis)
  - Endocrine abnormalities (hyperthyroidism)
  - Malignancy (neuroblastoma, ganglioneuroma)
- Conditions that compromise the efficiency of energy utilization
  - Chronic infection
  - Chronic renal disease
  - Hepatic insufficiency
  - Inborn errors of metabolism
  - Hormonal abnormalities
  - Certain genetic syndromes
  - Deficiencies of various micronutrients, including iron, zinc, and carnitine
- Conditions leading to deficiency in energy supply
  - Calories withheld.
  - In utero conditions.
  - Formula preparation mistakes.
  - Breastfeeding difficulties.
  - Parent-child psychosocial dysfunction.
  - Intentional abuse or neglect.
  - Poverty.
  - Unsound parental beliefs about nutrition.
  - Difficult feeders.
  - Calories not properly ingested or digested.
  - Anorexia (reflux esophagitis, emotional deprivation, chronic infection, dysphagia).
  - Subtle central nervous system abnormalities.
  - Structural abnormalities of the oropharynx or nasopharynx (cleft palate, choanal atresia, Treacher Collins syndrome, Pierre Robin sequence, laryngeal web).
  - Structural abnormalities of the gastrointestinal tract (stenosis or atresia of the esophagus or duodenum, tracheoesophageal fistula, vascular ring, strictures, achalasia, malrotation, antral web, pyloric stenosis).
  - Neuromuscular disorders (cerebral palsy, hydrocephalus, myopathies).
  - Conditions leading to excessive dyspnea (congestive heart failure, chronic lung disease).
  - Vomiting and rumination (structural abnormalities, increased intracranial pressure, chronic acidosis, gastroesophageal reflux).
  - Malabsorption.
    - Small bowel disease (celiac disease, inflammatory bowel disease, disaccharide malabsorption, intestinal lymphangiectasia, jejunal atresia, duplication cysts, chronic parasitic infections)
    - Pancreatic disease (cystic fibrosis, Shwachman-Diamond syndrome, chronic pancreatitis)
  - Liver disease (cirrhosis, intrahepatic cholestatic syndromes, biliary atresia).
  - Maternal depression has not been proven to be a risk factor in recent studies.

LABORATORY EVALUATION

- If the cause of the failure to thrive is not made clear by history and physical examination, laboratory investigation is unlikely to reveal it.
- In cases in which psychosocial features predominate, most laboratory tests may be unnecessary.
- If the cause of a child's failure to gain weight adequately remains uncertain after careful history and physical examination, a limited number of screening studies may be considered.
  - Complete blood cell count
  - Blood pH
  - Serum electrolytes
  - Blood urea nitrogen and creatinine
  - Urinalysis and urine culture

- Stool examination
  - Reducing substances
  - pH
  - Occult blood
  - Ova and parasites
- More extensive testing should be done only when historical or physical examination evidence indicates a specific diagnosis.

TREATMENT APPROACH

- The therapeutic approach to a child failing to gain weight adequately must be tailored to individual needs of the family and child.
- Therapy should be directed toward the underlying disease or condition where a specific diagnosis has been identified.
- When disturbance in the parent-child interaction is recognized as the cause of the patient's inability to gain weight, the family should be approached nonjudgmentally.
- Food avoidance behaviors may be altered by use of rewards.
- The severity of the child's condition should dictate the initial approach to treatment.

SPECIFIC TREATMENT

Mild to Moderate Undernutrition

- Goals.
  - Nutritional rehabilitation
  - Parental education
  - Behavioral intervention
- Infants and children exhibiting mild degrees of malnutrition (>80% of ideal body weight for age) may be managed
  - As outpatients
  - By primary care physician, with consultation from a nutritionist
    - Occasional consultation may be provided by subspecialist colleagues.
- Patients who have evidence of more severe caloric deprivation require involvement of a multidisciplinary team.
  - Primary care physician
  - Nutritionist
  - Mental health or behavioral therapist
  - Social worker
- Hospitalization may be necessary for a subset of these patients whose malnutrition is combined with or results from another significant medical condition.
- Home visitation by professionals may be a successful intervention in select circumstances.
- Child protective services must be alerted about any child thought to be the victim of neglect.
- Refeeding regimen.
  - ~10%–15% of calories from protein
  - 50%–60% from carbohydrate
  - 30%–40% from fat
- Attempts to overfeed malnourished infants at the outset of therapy should be avoided.
  - They may exhibit some degree of anorexia initially.
  - Refeeding that is too vigorous may induce malabsorption and diarrhea.
- A typical regimen has 3 phases.
  - Phase 1.
    - Begin with provision of 100% of daily age-adjusted energy and protein requirements based on the child's weight.
    - If this phase is well tolerated, proceed to phase 2.
  - Phase 2.
    - Intake is increased to provide adequate nutrition to achieve catch-up growth.
      - (Age-adjusted energy requirements [kcal/kg/d]) × (ratio of the child's ideal body weight for height)/(the child's actual body weight at presentation) = (reasonable estimate of the nutritional requirements for this stage).
        - The same calculation can be made for protein requirements.
      - Energy and protein requirements for infant refeeding usually can be accomplished with the use of a routine infant formula modified to increase its caloric density.
        - Mixing 13 oz of concentrated formula with 10 oz of water rather than 13 oz of water will create a formula that is 24 cal/oz *or*
        - Mixing 3 scoops of powdered formula with 5 oz water
      - Alternatively, carbohydrates in the form of glucose polymers or fat in the form of medium-chain triglycerides adds calories while avoiding complications of overhydration.
      - For older children, available caloric supplements will also include a wide variety of solid foods.

- Phase 3.
  - — Consolidation phase of nutritional rehabilitation
    - A varied diet is offered ad lib.
    - The child gradually approaches ideal body weight.
- Multivitamin and iron supplementation should be part of every refeeding regimen for undernourished children.

- Initiation of nutritional rehabilitation is an ideal time to educate parents and address family interactions, psychological vulnerabilities, and social needs.
  - Emphasis should be placed on appropriate nutritional information.
  - Concrete suggestions should be offered about how to structure mealtime at home.
    - — Minimize distractions.
    - — Provide a relaxed social environment that encourages good eating habits.
  - For families in need, access to community resources must be facilitated.
    - — Special Supplemental Nutrition Program for Women, Infants, and Children (WIC)
    - — Supplemental Nutrition Assistance Program (SNAP)
  - Pediatricians should be prepared to advocate vigorously for patients in need of supplemental nutrition or special infant formulas when families experience difficulties in obtaining these products.

Severe Undernutrition

- Hospitalize
  - Children who are <60% of ideal body weight for height
  - Children who fail to respond to appropriate outpatient management with adequate weight gain
- Important to avoid refeeding syndrome with its attendant morbidity.
- The nutritional rehabilitation
  - Will be more prolonged
  - May entail a period of tube feedings in addition to oral supplements
- In cases in which the gastrointestinal tract is temporarily inaccessible, parenteral feedings with central venous access may be necessary.
- Laboratory evaluation may need to be more intensive to monitor potential electrolyte disturbances following initial refeeding.

WHEN TO REFER

- If a diagnosis is made of a chronic disease pertaining to a subspecialty discipline such as cardiology, pulmonary medicine, nephrology, gastroenterology, or endocrinology
- If the psychosocial family dynamic indicates a need for psychiatric intervention for either or both parents
- If nutritional rehabilitation warrants the attention of a nutritionist
- If provider is concerned about intentional starvation or neglect, referral to child protective services

WHEN TO ADMIT

- Any child with a weight <60% of ideal body weight should be hospitalized.
  - Care should be provided by a multidisciplinary team.
    - — Nutritionists
    - — Social workers
    - — Pediatricians
    - — Pediatric subspecialists, when appropriate
- Other children who should be hospitalized include
  - Any child who, despite appropriate outpatient management, continues to fail to gain weight at an acceptable rate
  - Any child who presents with signs of marasmus or severe protein malnutrition (kwashiorkor)
  - Any child who would benefit from a period of close, continuous monitoring

FOLLOW-UP

- Poor weight gain in infancy should be followed up assiduously.
- Initial weekly visits for infants may be necessary to reassure the parents and practitioner that the therapy undertaken is having the desired effects.
- Infants <6 months, when provided with adequate calories, begin to gain weight in a few days.
- Older children may take longer than their younger counterparts before sustained weight gain is established.
- Ongoing developmental, behavioral, and social evaluations must be incorporated into any plan for follow-up.
  - Children who gain weight poorly often have abnormalities in these areas.
  - The lingering effects of calorie, protein, and micronutrient deprivation may manifest as developmental and behavioral abnormalities.
    - — Such results are particularly likely in children whose mothers exhibit affective disorders.

- Intense interventions, at least in controlled circumstances, attenuate anthropometric deficiencies from significant undernutrition in infancy.

COMPLICATIONS

- Most children who fail to gain weight adequately suffer from malnutrition and are therefore at risk for its attendant consequences.

PROGNOSIS

- Caution must be used when predicting outcomes for children who have abnormal weight gain patterns in infancy and childhood.
- A variety of conditions may give rise to this clinical picture.
  - High-quality data on which reasonable predictions might be sustained are lacking.
  - One systematic review of 13 long-term longitudinal studies concluded that growth and neurocognitive outcomes probably do not differ substantially between children with failure to thrive and their unaffected peers.
  - In an extensive review of the literature, the Agency for Healthcare Research and Quality concluded that children with failure to thrive in infancy are likely to suffer immunologic, behavioral, cognitive, and psychomotor developmental deficits that persist despite interventions.
- Such disparate findings suggest that most children in the mild failure to thrive category will
  - Experience brisk nutritional rehabilitation.
  - Do well with adequate follow-up.
- More severely affected children may require more prolonged or repetitive interventions.
  - Type of intervention depends on the underlying cause.
  - These children may suffer residual cognitive, behavioral, and educational consequences.
- All children who exhibit faltering weight gain during infancy and childhood absolutely must receive early comprehensive evaluation and prompt treatment.

Fatigue and Weakness

DEFINITION

- *Fatigue* and *weakness*
  - May or may not be related to medical diagnoses
  - Used commonly in medical and colloquial language
  - Difficult to define and sometimes used interchangeably
- Adolescents and children often use other terms to describe perceptions of somatic weakness and fatigue.
- *Fatigue* involves
  - Extreme and unusual tiredness
  - Decreased physical performance
  - Excessive need for rest
  - Often is accompanied by feelings of sleepiness, weariness, irritability, lassitude, boredom, or decreased efficiency
- *Weakness* refers to diminished body or muscle strength (ie, inability to generate or maintain force [stamina]).
  - Identified only by demonstration of abnormal neurologic or muscular function based on history, physical examination, and laboratory studies
  - In infants, often suggests hypotonia
  - In older children and adolescents, may be described as trouble running, keeping up in gym class, clumsiness, or lack of agility

HISTORY

- Goals.
  - Rule out underlying medical illness.
  - Return the child to a state of well-being.
  - Relieve parental concerns.
- Critical evaluation of history, physical examination, and laboratory tests should enable quick determination of causes for fatigue.
- Points to consider include
  - Adequate time and concern are needed to evaluate history.
  - Symptoms of chronic fatigue cannot be dismissed casually over the telephone or with a quick office visit.
  - The problem may seem insignificant, but the child or parents are worried about the fatigue.
    - Family members may disagree about the significance of the symptoms.
  - Patients who come to the primary care physician complaining of fatigue often have emotionally based problems.
    - A careful history, with information from the child and parents (taken separately when appropriate), often helps narrow the differential diagnosis.
    - Discrepancies between the child's and the parents' observations become evident.
    - Emotional stress or some disruption in the patient's life is often part of the history.
    - In most cases, a diagnosis of emotionally related fatigue emerges on the basis of the history alone.
    - Information derived from a long-standing physician-patient relationship helps reduce tensions during the evaluation.
  - Fatigue is rarely pertinent in infants.
    - With a serious underlying condition, infants might be described as "listless," "tiring during feeding," or "droopy."
    - Young children infrequently complain of feeling fatigued.
  - Before adolescence, most children cannot verbalize a feeling of fatigue.
    - Even with chronic diseases, most children do not express fatigue verbally.
    - Younger children occasionally express a sense of lassitude and fatigue on questioning.
  - Fatigue is usually exhibited in terms of a child's physical activity and performance in school, sports, and other organized activities.
    - The problem may be manifested by trouble running or keeping up in gym class, clumsiness, or lack of agility.
  - Concerned parents usually report that the child appears fatigued.
    - "He has no energy."
    - "She lies around all the time."
    - "She seems bored and droopy."
    - "He's sleeping a lot of the time."
    - "She has no pep."
    - "He drags around."
    - "I can't get her to do a thing."
  - The younger the child, the more likely that the expressed or observed fatigue has a pathological basis.

- Chronic fatigue is common among adolescents.
  - Even minor illnesses often precipitate prolonged fatigue in adolescents.
  - Parents often perceive their adolescent children to be fatigued, even when the adolescents do not agree.

PHYSICAL EXAMINATION

- Thorough physical examination may be the only assessment necessary.
- In all age groups
  - Search for sites of chronic latent infection.
    - Adenopathy
      - Cervical adenopathy can be a clue to the diagnosis of infectious mononucleosis
    - Enlargement or tenderness of the liver and spleen
    - Abdominal masses
  - Prolonged fever, however low grade, must always be viewed as significant and may suggest
    - Infection
    - Inflammatory disease
    - Cancer
  - Palpate for an enlarged or tender thyroid gland.
  - Look for mild scleral icterus and petechiae.
  - Examine for pallor from
    - Anemia
    - Hypothyroidism
  - Examine the oropharynx for hyperpigmentation of gums and buccal mucosa (Addison disease).
  - Assess plotted height and weight.
    - Failure to progress along expected growth parameters may indicate an underlying systemic process.
      - Chronic cardiac disorder
      - Pulmonary disorder
      - Gastrointestinal disorder
      - Renal disorder
    - Poor growth velocity and obesity may indicate underlying endocrinopathy.
      - Hypothyroidism
      - Cushing syndrome
    - In adolescents with unexplained fatigue, poor weight gain may be a manifestation of inflammatory bowel disease.
  - A young child's affect and appearance are most revealing.
  - Adolescents may be more difficult to evaluate and may
    - Be slovenly.
    - Be uncommunicative.
    - Be depressed.
    - Be unwilling to express their feelings.
    - Appear physically ill.

DIFFERENTIAL DIAGNOSIS

Fatigue

Infants

- Infants with cyanotic or congestive heart disease
  - Often appear to tire easily.
  - Sweat excessively and tire with feedings.
- Other serious conditions, including severe anemia and hypothyroidism, may present as listlessness.

Children

- Recurrent or chronic infection is the most common cause.
  - Otitis media, sinusitis, and tonsillitis of a recurrent and smoldering nature
    - Often overlooked for systemic effects.
    - Fatigue may be prominent.
- Upper respiratory tract allergies.
  - Often mistakenly considered insignificant
  - May cause impressive fatigue, irritability, and mild depression
- Endocrine disorders.
  - Only hypothyroidism is likely to be associated with fatigue.
    - A child with hypothyroidism whose growth rate has decreased may exhibit increasing fatigue and lassitude, at first subtle, as the only symptoms.
  - Thyrotoxicosis is uncommon in young children but occasionally produces isolated fatigue in adolescents.
  - Diabetes mellitus.
    - Any metabolic disorder can cause fatigue, but only diabetes mellitus occurs with enough frequency to merit consideration.
    - Fatigue almost always accompanies an initial or uncontrolled diabetic state.
- Inflammatory diseases.
  - Juvenile idiopathic arthritis and other rheumatoid-like disorders, such as Lyme disease
    - Significant fatigue out of proportion to the child's musculoskeletal symptoms
  - Rheumatic fever
- Pulmonary disease.
  - Chronic advanced pulmonary disease, such as cystic fibrosis.
  - Underlying disease is usually readily evident before fatigue becomes severe.
  - Severe fatigue may be caused by a previously undiagnosed hypoxic disorder.

- Immunologic disorders.
  - AIDS
- Chronic renal disease.
- Anemia.
  - Often thought to be cause of fatigue, but generally not the case.
  - Symptoms are usually not seen in children until the hemoglobin level decreases to 6 or 7 g/dL.
    - If erythrocyte counts decrease gradually, even lower hemoglobin levels may ensue without clinically evident symptoms.
    - Younger children especially seem to tolerate markedly low hemoglobin levels with no symptoms.
- Malignancy.
  - Leukemia or lymphoma occasionally develops insidiously, with fatigue as the major symptom.
- Obstructive sleep apnea.
- Emotional disorders.
  - Most children experience brief, transient periods of lassitude or fatigue that are usually self-limited.
  - Unexplained chronic fatigue is often found to be emotionally related.
  - Before adolescence, the complaint usually stems from the parents' concern about a child's reduced activity level.
  - A younger child will be noted to
    - Prefer sedentary activities
    - "Lie around the house a lot"
    - Appear tired
    - Lack energy
    - Shrink from social contacts
  - Observed traits may have been long-standing.
    - A comment from grandparents or a teacher may arouse parental anxiety and precipitate a visit to the primary care physician.
    - The family usually suspects that the child has a serious organic disease.
    - Further evaluation usually reveals that the child is performing very satisfactorily but not up to the family's excessive expectations.
    - The child may be withdrawing because of
      - Failure to compete with an exceptional sibling
      - Real or imagined failure in school
    - A child may feel a lack of well-being because of parental discord.
    - Lack of parental involvement with a child may lead to lassitude and boredom.
  - Stress and anxiety in children often result in hyperactivity or withdrawal.
    - The more common withdrawal reaction may express itself as chronic fatigue.
    - Protracted and severe periods of withdrawal are more likely to be caused by a pathological process.
  - In some children, chronic fatigue may be a sign of true psychiatric depression.

Adolescents

- Chronic fatigue is encountered most frequently in adolescents.
- Even minor illnesses often precipitate prolonged fatigue in adolescents.
- Normal swings of mood and energy are usually of more concern to parents and teachers than to the patient.
  - However, some adolescents initiate visits to their primary care physician because they feel fatigue.
- Viral or parasitic illnesses.
  - *Mycoplasma pneumoniae* infection, often low grade and without fever
  - Hepatitis, cytomegalovirus, toxoplasmosis
  - Infectious mononucleosis
    - Most adults and many infants and children have been infected with the Epstein-Barr virus (EBV).
    - Clinical manifestations in proved cases are extremely variable.
    - Some patients remain symptom free.
    - Symptoms usually resolve in several weeks, but the occasional patient may have an atypical or more prolonged course.
      - Initial clinical findings persist or are intermittent over months or, in rare cases, years, and typically include chronic fatigue.
      - The terms *chronic infectious mononucleosis* and *chronic fatigue syndrome* (CFS) have become widely popular but are often misused and can lead to mild mass hysteria among adolescents convinced they suffer from such a condition.
- Other conditions.
  - Autoimmune disease: Children with autoimmune disease may initially have fatigue with little else.
    - Addison disease should be considered in unexplained fatigue associated with
      - Weakness
      - Anorexia
      - Nausea and vomiting
      - Weight loss

- Children may have prolonged symptoms, including fatigue, without any physical findings with
  - Inflammatory bowel disease
    - Unexplained fatigue may continue for months as the only major symptom.
    - Eventually accompanied by fever, abdominal symptoms, and abnormal stools.
  - Arthritis or arthritis-like illness
    - Mild articular or periarticular inflammation may be missed on physical examination.
- Alcoholism and substance use.
  - Possible cause of chronic fatigue that should not be overlooked in this age group
- Thyroid disease.
  - Enlarged tender thyroid gland and fatigue may indicate thyroiditis with emerging hypothyroidism.
  - The thyroid gland is often palpable and full in healthy adolescents.
- Malignancy (especially leukemia).
- Anemia.
  - Anemia accompanied by thrombocytopenia suggests leukemia or aplastic anemia.

- Emotional disorders.
  - Fatigue.
  - Lassitude.
  - Lack of energy.
  - Mild depression.
  - May be sleep deprived, have unhealthy eating habits.
  - Hypochondriacal symptoms.
  - Possible fever, usually caused by infection (eg, infectious mononucleosis, influenza).
    - Emotional reaction may be precipitated by a physical illness, particularly infection.
  - Usually seen during periods of greatest stress.
    - May collapse with fatigue after intense and exuberant activity (eg, schoolwork, extracurricular activity, sports, social events)
  - Burnout and fatigue are common in over-achieving high school and college students.
- CFS.
  - Initially attributed to infection with EBV.
  - Symptoms include
    - Persistent or relapsing severe fatigue
    - Fever
    - Headache
    - Sore throat
    - Tender lymphadenitis
    - Nausea or vomiting
    - Myalgia
    - Arthralgia
    - Abdominal pain
  - Neurocognitive symptoms, such as
    - Inability to concentrate
    - Sleep disturbances
    - Episodic confusion
    - Memory problems
    - Depression
    - Anxiety
    - Irritability
  - Neurocognitive symptoms are the most difficult to evaluate because of individual differences in emotional perception.
  - Extensive laboratory evaluations usually produce results within reference ranges.
  - Centers for Disease Control and Prevention (CDC) criteria for the case definition of CFS (based mainly on observations in adults).
    - New onset of persistent or relapsing fatigue lasting ≥6 months.
    - No prior history of such fatigue.
    - Exclusion of other clinical conditions that might produce similar symptoms.
    - In addition, symptoms must include ≥4 of the following features
      - Muscle pain
      - Tender lymphadenopathy
      - Headaches of new type, pattern, or severity
      - Arthralgia
      - Impaired memory or concentration
      - Pharyngitis
      - Low-grade fever
      - Post-exertional malaise lasting >24 hours
      - Sleep disturbances
    - Individuals with >6 months of disabling fatigue but an insufficient number of symptoms to meet criteria have been labeled as having idiopathic chronic fatigue.
    - CDC criteria exclude most past or current major psychiatric disorders but allow some comorbid psychiatric symptoms (eg, anxiety, non-melancholic depression).

Weakness

Infants

- Infants with weakness are often described by parents as being "floppy."
  - In the newborn period, some may assume a frog-leg position.

- Usually indicates hypotonia caused by a neuromuscular disorder.
- Genetic disorders are among the more common causes of hypotonia in infants.
  - Down syndrome
  - Congenital hypothyroidism
  - Infantile form of spinal muscular atrophy (Werdnig-Hoffmann disease)
- Infant botulism.
  - Caused by ingesting *Clostridium botulinum* spores
    - Honey is a common source.
  - Can cause floppy appearance accompanied by
    - A weak cry caused by muscle weakness
    - Loss of head control
    - Lethargy
    - Inability to feed
    - Constipation

Older Children and Adolescents

- Myasthenia gravis and Guillain-Barré syndrome (postinfectious polyneuropathy)
  - Perhaps the 2 most common causes of weakness in this age group.
  - In myasthenia gravis, deep-tendon reflexes may be diminished but are rarely absent.
  - Guillain-Barré syndrome is remarkable for bilateral, symmetrically absent tendon stretch reflexes.
- Other causes of weakness in the older child include
  - Muscular dystrophies
  - The juvenile form of spinal muscular atrophy
  - Dermatomyositis
  - Polymyositis

LABORATORY EVALUATION

- Initial laboratory evaluation can include
  - Complete blood cell count with erythrocyte indices
  - Thyroid and liver function tests
  - Throat culture
  - Stool examination for blood
  - Cold agglutinin test (simple screen for *Mycoplasma* infection)
  - Erythrocyte sedimentation rate (ESR)
    - The most valuable screening test for inflammatory diseases of all varieties.
    - Reference sedimentation rate almost always rules out
      - Autoimmune disease
      - Inflammatory bowel disease
      - Chronic smoldering infections
      - Disseminated malignancies
    - Elevated ESR requires further investigation.
- Routine urinalysis
  - Almost always reveals diabetes.
  - Most patients who have chronic renal failure have abnormal urinalyses, as well as significant anemia.
  - Confirm these diagnoses with
    - Measurement of blood glucose in diabetes
    - Measurement of creatinine or blood urea nitrogen in renal disease
- Anemia
  - Erythrocyte indices and reticulocyte count will characterize the anemia and suggest its possible causes.
- Thyroid disease can usually be ruled out quickly with
  - A thyroid-stimulating hormone test
  - A free T_4 test
- Infectious mononucleosis
  - Results of the heterophil antibody test may be negative in many young children and infants and ~10% of older children and adolescents with the disease.
  - Reliability of EBV antibody testing can confirm active infectious mononucleosis.
  - EBV antibody titers can usually differentiate long-past infection from recent and active infection.
    - Eliminates EBV infection and infectious mononucleosis as causes for the fatigue
    - Permits a search for other likely neuropsychiatric causes
- Toxoplasmosis or cytomegalovirus can be confirmed by
  - Positive results of a fluorescent antibody test
  - Negative results of a heterophil antibody test
- Adrenocorticotropic hormone stimulation test
  - Definitive diagnostic test for Addison disease.
  - Hyperkalemia, hyponatremia, and hypoglycemia are useful diagnostic features.
- Laboratory studies for muscle weakness may include
  - Chromosomal studies
  - Muscle enzyme assays

DIAGNOSTIC PROCEDURES

- Depending on suspected diagnosis, evaluation of a patient who has weakness may include
  - Nerve conduction studies
  - Electromyography
  - Edrophonium (Tensilon) test
  - Muscle biopsy
  - Lumbar puncture
  - Consultation with a pediatric neurologist

TREATMENT APPROACH

- After significant organic disease is ruled out, in most patients further management requires meaningful communication among the pediatrician, patient, and parents.
- Conversation after the physical examination, with appropriate give and take, should
  - Reassure the patient that she or he is basically healthy.
  - Reiterate how common and normal the occurrence of fatigue is.
  - Review daily routines and stresses.
  - Suggest modifications of lifestyle and approach to life's situations.
- Appropriate parental expectations must be emphasized.
- The normal variability in performance and behavior of healthy younger children must be kept in mind.
- Older children and adolescents benefit from personal, warm attention and a continuous relationship with one physician.

SPECIFIC TREATMENT

- If emotional fatigue is thought to exist
  - The patient (especially adolescents) must be made to understand that organic diseases have been ruled out.
  - The patient must be made aware of emotional basis for the fatigue.
  - Reasons for any psychiatric referral must be made clear.
- Treatment for organic diseases is specific to each.

WHEN TO REFER

- Unexplained weight loss
- Hypotonia in infants
- Suspected major affective disorder
- Suspected malignancy

WHEN TO ADMIT

- Severe depression or suicidal ideation
- Need for evaluation of neuromuscular disorders, including
  - Spinal muscular atrophy
  - Guillain-Barré syndrome
  - Myasthenia gravis

PROGNOSIS

- CFS
  - Although few longitudinal data are available, the prognosis for adolescents with CFS is better than that for adults.
  - Symptoms may persist for months or several years, but most adolescents with CFS have a good outcome.
    - Complete recovery in ~50%

DEFINITION

- Fetal alcohol spectrum disorder (FASD)
  - Continuum of physical, growth, and neurobehavioral abnormalities that occur as a result of prenatal exposure to alcohol
  - Well-defined set of clinical diagnostic criteria
    - Characteristic dysmorphic facial features
    - Evidence of growth restriction
    - Neurocognitive deficits
    - Presence of definite or unknown prenatal alcohol exposure
- Other disorders in the fetal alcohol spectrum
  - Partial fetal alcohol syndrome (PFAS)
  - Alcohol-related birth defects (ARBDs)
  - Alcohol-related neurodevelopmental disorder (ARND)
  - Neurodevelopmental disorder associated with prenatal alcohol exposure (ND-PAE)
    - Introduced in *Diagnostic and Statistical Manual of Mental Disorders*, 5th Edition.
    - Roughly equivalent to ARND.
    - Diagnostic criteria include evidence of "more than minimal" alcohol exposure during pregnancy and impairments in cognition, self-regulation, and adaptive functioning.

SIGNS AND SYMPTOMS

- Fetal alcohol syndrome (FAS) diagnostic criteria.[1]
  - 3 midline characteristics are discriminant for FAS.
    - Short palpebral fissure length (<10th percentile for age)
      - Measured from the inner corner to the outer corner of the eye while the patient's eyes are open
      - Plotted on a nomogram to determine the standard deviation (SD) from the mean based on the patient's age
    - Smooth philtrum (University of Washington Lip-Philtrum Guide score of 4 or 5)
    - Thin upper lip (University of Washington Lip-Philtrum Guide score of 4 or 5)
  - Other physical features or anomalies commonly seen in FASD, but not at a frequency or specificity high enough to warrant inclusion as diagnostic criteria, include
    - Epicanthal folds
    - Ptosis
    - Upturned nose
    - Flat nasal bridge
    - Midface hypoplasia
    - Underdeveloped ears (with a "railroad track" appearance, where there is a prominent superior crus of the helix and parallel inferior crus of the antihelix)
    - Nail hypoplasia
    - Small and large joint contractures
    - Clinodactyly of the fifth fingers
    - "Hockey stick" palmar creases (Upper transverse crease widens and ends between the second and third digits.)
    - Hirsutism
    - Congenital cardiac defects
  - Growth.
    - Measured using standard height/weight measurements and growth curves.
    - Deficiency is defined as height or weight ≤10th percentile for age and gender as documented at any time from birth, as long as poor growth is not secondary to postnatal influences (eg, chronic illness, malnutrition).
  - Structural, neurologic, or functional abnormalities in the central nervous system (CNS).
    - Structural anomalies can include microcephaly (head circumference ≤10th percentile for age/gender) or clinically significant brain abnormalities of presumed prenatal onset identified on imaging studies.
    - Frequent structural CNS anomalies in FASD include
      - Abnormal cerebellum (particularly of the cerebellar vermis)
      - Abnormal corpus callosum (agenesis, partial agenesis, hypoplasia/thinning)
      - Abnormal basal ganglia
      - Overall reduction in brain volume
    - Neurologic criteria can be fulfilled by the presence of seizures (not attributable to postnatal events) or abnormal findings on neurologic examination.
    - Functional deficit criteria.
      - Global cognitive deficit (eg, low IQ, global developmental delay)
        - Difficulties (scores >1 SD below the mean on standardized testing) in ≥3 of the following areas:
          - Cognition/development (eg, specific learning disabilities, poor processing, discrepancy between verbal and nonverbal skills)
          - Executive functioning
          - Motor functioning
          - Inattention or hyperactivity

- Social skills
- Other (eg, sensory problems, memory deficits)

— Determination of functional CNS abnormalities typically requires formal neuropsychological or other developmental testing.

- Confirmed maternal use of alcohol during pregnancy is not required for a diagnosis of FAS in the presence of all 3 of the previously listed criteria (facial features, growth, and CNS abnormalities).
- In cases of children who have been adopted or are in foster care placement, information about the prenatal history may not be available.
- In the absence of self-reported maternal history, documentation of exposure could include
  - — Direct observations by others
  - — Birth records that may note maternal alcohol use or maternal blood alcohol
  - — History of alcohol-related events (eg, arrests for driving under the influence, alcohol abuse treatment) during the pregnancy
- The diagnosis of ARBD, ARND, or the newly defined ND-PAE does require confirmed maternal alcohol use.

■ PFAS with confirmed maternal alcohol exposure requires all 3 of the following criteria:
- Confirmed maternal alcohol exposure
- At least 2 of the following facial characteristics:
  - — Small palpebral fissure length (≤10th percentile)
  - — Thin vermilion border of the upper lip (University of Washington Lip-Philtrum Guide score of 4 or 5)
  - — Smooth philtrum (University of Washington Lip-Philtrum Guide score of 4 or 5)
- One of the following conditions:
  - — Height or weight ≤10th percentile for age, sex, and ethnicity
  - — Evidence of structural CNS abnormalities, including ≥1 of the following:
    - ■ Head circumference ≤10th percentile
    - ■ Structural brain abnormalities
  - — Evidence of a complex pattern of behavioral or cognitive abnormalities inconsistent with developmental level that cannot be explained by genetic predisposition, family background, or environment alone
    - ■ Marked impairment in performance of complex tasks
    - ■ Higher-level receptive and expressive language deficits
    - ■ Disordered behavior

■ ARBD requires all 3 of the following criteria:
- Confirmed maternal alcohol exposure
- ≥2 of the following facial characteristics:
  - — Small palpebral fissure length (≤10th percentile)
  - — Thin vermilion border of the upper lip (University of Washington Lip-Philtrum Guide score of 4 or 5)
  - — Smooth philtrum (University of Washington Lip-Philtrum Guide score of 4 or 5)
- Congenital structural defects in ≥1 of the following categories, including malformations and dysplasias (if the patient displays minor anomalies only, ≥2 must be present):
  - — Cardiac: atrial septal defects, aberrant great vessels, ventricular septal defects, conotruncal heart defects
  - — Skeletal: radioulnar synostosis, vertebral segmentation defects, large joint contractures, scoliosis
  - — Renal: aplastic/hypoplastic/dysplastic kidneys, horseshoe kidneys, ureteral duplications
  - — Ocular: strabismus, ptosis, retinal vascular anomalies, optic nerve hypoplasia
  - — Ears: conductive hearing loss, sensorineural hearing loss
  - — Minor anomalies: hypoplastic nails, short fifth digits, fifth finger clinodactyly, pectus carinatum or excavatum, camptodactyly, "hockey stick" palmar creases, refractive errors, "railroad track" ears

■ ARND requires both of the following conditions:
- Confirmed maternal alcohol exposure *and*
- ≥1 of the following conditions:
  - — Evidence of deficient brain growth or abnormal morphogenesis, including ≥1 of the following:
    - ■ Structural brain abnormalities
    - ■ Head circumference ≤10th percentile for age and sex
  - — Evidence of a complex pattern of behavioral or cognitive abnormalities inconsistent with developmental level that cannot be explained by genetic predisposition, family background, or environment alone, including
    - ■ Marked impairment in performance of complex tasks
    - ■ Higher-level receptive and expressive language deficits
    - ■ Disordered behavior

- Recognition of CNS features of FASD requires familiarity with manifestation of neurobehavioral features of FASD at different ages.
  - Infants and toddlers may have difficulty with self-soothing and be prone to overstimulation.
  - Poor feeding is common in young infants with FASD.
  - Sleep problems, difficulties with language comprehension, and poor problem-solving abilities may emerge in young childhood.
  - Older, school-aged children are more likely to present with specific learning disabilities, poor social skills (eg, social immaturity, lack of social boundaries), and poor adaptive skills.
  - Facial characteristics of FASD often change over time and may become less apparent as the patient approaches adulthood.
    - Review of photographs from early childhood may aid in the diagnosis.

DIFFERENTIAL DIAGNOSIS

- The individual facial and other physical features that are characteristic of FASD are not unique and may overlap with those seen in many other teratogenic and genetic syndromes (**Tables 1** and **2**).
- Combination of 3 facial features (smooth philtrum, thin vermilion border, and small palpebral fissures, as defined by the 4-digit FASD diagnostic code) is >95% specific to FAS and prenatal alcohol exposure.
- Teratogenic syndromes with features that most closely overlap (or co-occur) with FASD include
  - Fetal valproate syndrome
  - Maternal phenylketonuria effects
  - Toluene embryopathy
- The presence or absence of other associated dysmorphisms can often help the physician formulate an appropriate differential diagnosis.
  - Some of the facial features commonly seen in FASD can also occur in a wide range of specific single-gene syndromes or chromosome abnormalities.
  - Growth restriction and CNS abnormalities are common in many teratogenic and genetic syndromes.
- In some cases, specific chromosomal or single-gene testing may be indicated to evaluate for alternate diagnoses.

DIAGNOSTIC APPROACH

- The diagnosis of FAS and other FASD lies primarily in the history and physical examination.
- Other specific evaluations or tests, such as a neuropsychological evaluation and, sometimes, neuroimaging or other neurologic testing (eg, electroencephalography [EEG]), play a supportive role.
- No single consensus guideline for the diagnosis of FASD.
  - Multiple published guidelines exist but are not consistent.
- The American Academy of Pediatrics (AAP) developed a schema in collaboration with the Centers for Disease Control and Prevention for early and streamlined identification of FASD in the medical home.
  - All children should be screened for developmental and growth concerns in the context of the well-child evaluation.
  - A history of prenatal alcohol exposure and other risk factors should be sought as part of the comprehensive patient history.
  - Any child with FASD signs or symptoms, risk factors for FASD, or parental concern for FASD should prompt additional evaluation by the pediatrician for
    - CNS abnormalities
    - Growth deficits
    - Characteristic facial features
- Referrals to specialists for further diagnostic investigations are indicated in certain circumstances.
  - If the patient has growth restriction or any dysmorphic facial features but no documented CNS abnormalities, referral to a geneticist is indicated for evaluation for possible alternate diagnoses.
  - If the patient has CNS abnormalities but does not fulfill all of the other facial, growth, and alcohol exposure criteria for FAS, referral to a FASD clinic or other appropriate specialist(s) (eg, neurologist, geneticist, developmental pediatrician, neuropsychologist) is indicated.
  - Referral to early intervention or school-based developmental services is warranted in any patient with evidence of CNS abnormalities.

Table 1. Selected Differential Diagnosis for Individual Features Associated With Fetal Alcohol Spectrum Disorder

Feature	Associated Syndromes (Other Than FASD)
Smooth philtrum	Toluene embryopathy
	Maternal phenylketonuria effects
	Floating-Harbor syndrome
	X-linked Opitz G/BBB syndrome
	Geleophysic dysplasia
	Williams syndrome
Thin upper lip	Maternal phenylketonuria effects
	Toluene embryopathy
	de Lange syndrome
	Miller-Dieker syndrome
	Fetal valproate effects
Short palpebral fissures	Maternal phenylketonuria effects
	Toluene embryopathy
	Dubowitz syndrome
	FG syndrome
	X-linked Opitz G/BBB syndrome
	Williams syndrome
	Feingold syndrome
Neurobehavioral features	22q11.2 deletion syndrome (DiGeorge syndrome, velocardiofacial syndrome)
	Fragile X syndrome
	Turner syndrome
	16p11.2 deletion syndrome
	10p deletion syndrome
Prenatal and postnatal growth delay	Associated with many chromosomal and single gene syndromes (too numerous to list)

Abbreviation: FASD, fetal alcohol spectrum disorder.

Adapted from Bertrand J, Floyd RL, Weber MK, et al. *Fetal Alcohol Syndrome: Guidelines for Referral and Diagnosis.* Atlanta, GA: Centers for Disease Control and Prevention, 2004; and Senturias Y, Asamoah A. Fetal alcohol spectrum disorders: guidance for recognition, diagnosis, differential diagnosis and referral. *Curr Probl Pediatr Adolesc Health Care.* 2014;44(4):88–95.

Table 2. Differential Diagnosis of Fetal Alcohol Spectrum Disorder and Distinguishing Features

Condition	Overlapping Features With FASD	Distinguishing Features From FASD
22q11.2 deletion syndrome (DiGeorge syndrome, velocardiofacial syndrome)	Ptosis, cardiac defects (much more common in the 22q11 deletion), learning difficulties, speech delay, short stature, short palpebral fissures (occasionally)	Palatal defects, immune dysfunction, hypocalcemia; smooth philtrum and thin upper lip not typically seen
Dubowitz syndrome	Growth delay (prenatal onset), microcephaly, short palpebral fissures, ptosis	Eczema; high-pitched, hoarse cry; genital anomalies in males; syndactyly and other limb anomalies
Maternal phenylketonuria effects	Microcephaly, short palpebral fissures, long and smooth philtrum, thin upper lip	History of phenylketonuria in mother; intellectual disability is typically severe; rounded facies; short, upturned nose.
de Lange syndrome	Prenatal and postnatal growth delay, thin upper lip	Synophrys, long eyelashes, high arched palate, limb anomalies
Toluene embryopathy	Short palpebral fissures, smooth philtrum, thin upper lip	Large anterior fontanel, micrognathia, bifrontal narrowing, down-turned corners of the mouth
Floating-Harbor syndrome	Short stature, smooth philtrum, thin lips, ADHD, learning disabilities	Long nose with narrow bridge, full tip, and an overhanging columella; triangular facies; deeply set eyes; philtrum is usually short.
Feingold syndrome	Short stature, microcephaly, short palpebral fissures, cardiac defects, learning disabilities	Gastrointestinal atresia, finger/toe anomalies (syndactyly, brachymesophalangy)
Fetal valproate effects	Epicanthal folds, thin upper lip, long and smooth philtrum, variable learning disabilities	Tall forehead, trigonocephaly, bifrontal narrowing, infraorbital creases, neural tube defects
Geleophysic dysplasia	Thin upper lip, long and smooth philtrum, short stature	Round and full face, coarsening of facial features over time, thick skin, joint contractures
Miller-Dieker syndrome	Thin upper lip	Vertical ridging and furrowing in the central forehead, bitemporal narrowing, severe neurologic features (eg, seizures, intellectual disability)
FG syndrome	Short palpebral fissures, short stature	Macrocephaly, tall forehead, downward-slanting palpebral fissures, small ears, constipation
X-linked Opitz G/BBB syndrome	Learning disabilities, microcephaly, smooth philtrum, short palpebral fissures	Prominent forehead, widow's peak, cleft lip/palate, laryngotracheoesophageal defects, genital anomalies

Table 2 (*continued*)

Condition	Overlapping Features With FASD	Distinguishing Features From FASD
Fragile X syndrome	ADHD, learning disabilities	Frequent ASD, more severe intellectual disability (in males), long face, prominent ears, joint laxity, macroorchidism
Turner syndrome	ADHD, learning disabilities, short stature	Females only; does not share craniofacial features with FASD; ovarian dysgenesis, cardiac defects (aorta coarctation, bicuspid aortic valve), short neck, low posterior hairline, broad chest

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; ASD, autism spectrum disorder; FASD, fetal alcohol spectrum disorder.

Adapted from Bertrand J, Floyd RL, Weber MK, et al. *Fetal Alcohol Syndrome: Guidelines for Referral and Diagnosis.* Atlanta, GA: Centers for Disease Control and Prevention, 2004; and Senturias Y, Asamoah A. Fetal alcohol spectrum disorders: guidance for recognition, diagnosis, differential diagnosis, and referral. *Curr Probl Pediatr Adolesc Health Care.* 2014;44(4):88–95.

LABORATORY FINDINGS

- Diagnostic laboratory studies, such as molecular genetic testing, may be indicated to exclude other diagnoses with overlapping features.

IMAGING

- Imaging is not routinely indicated.
- Intracranial imaging (ultrasound, computed tomography, or magnetic resonance imaging) may be performed because of microcephaly, seizures, or severe intellectual deficits.
- Where clinical history or physical examination suggests cardiac, renal, or spinal (eg, tethered cord) anomalies, specific imaging studies may be indicated.

DIAGNOSTIC PROCEDURES

- EEG when there is clinical suspicion of seizures.
- Neuropsychological testing is often needed to direct management.

TREATMENT APPROACH

- First step is early and accurate diagnosis.
  - Diagnosis <6 years is associated with a more favorable outcome and lower prevalence of secondary disabilities.
- The AAP *Fetal Alcohol Spectrum Disorders Toolkit* includes lists of resources for parents, educators, and physicians, including informational handouts, example care plans, and referrals to outside agencies.
- Patients who have a diagnostic evaluation in a multidisciplinary FASD diagnostic clinic will typically be seen by multiple specialists.
  - Developmental pediatricians
  - Neurologists
  - Geneticists
  - Social workers
  - Physical and occupational therapists
  - Speech-language pathologists
  - Psychologists or neuropsychologists
- Pediatricians may choose to refer their patients to any of these specialists individually, based on the child's specific needs.
- Because no single treatment plan applies to all children with FASD, the pediatrician's main role is frequently as care coordinator.
- The pediatrician should fully assess and frequently update the child's medical needs.
- Poor growth is common, warranting careful monitoring of growth or evaluation by a nutritionist.
- Children should be screened periodically for vision, hearing, and sleep difficulties.
- Nearly all patients with FASD can benefit from developmental assessment by
  - Early intervention services (<3 years)
  - School system (>3 years)
  - Neuropsychologist, psychologist, or developmental pediatrician

- Without focusing on assigning blame, parents should be educated about the underlying cause for FASD.
  - If appropriate, the biological mother may be offered referral to counseling or alcohol use disorder treatment services.
  - If the family unit is severely dysfunctional, alternative placement of the child may be considered.
  - Family counseling may be indicated.
- Proper neuropsychological assessment allows the child's specific educational and behavioral needs to be more precisely defined, which can be invaluable for educators.
- All children with a diagnosis of FASD qualify for services under the Individuals With Disability Education Act.
- Some children with FASD may need special education services for intellectual or learning disabilities.
- While many children with FASD have IQ or other developmental quotients within the normal range, specific deficits (eg, in memory, executive functioning, behavior regulation) may impair school performance.
- The AAP FASD toolkit lists evidence-based educational and behavioral interventions (**Table 3**).

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Table 3. Evidence-Based Educational and Behavioral Interventions Specific for Fetal Alcohol Spectrum Disorder

Program	Overview	Outcomes
Math Interactive Learning Experience (MILE), Emory University, Atlanta, GA	6-week mathematics learning program providing an active learning approach for children; workshops for caregivers providing information on FASD and learning strategies	Improved math skills and decreased problem behaviors
Good Buddies, University of California at Los Angeles	12 weekly separate sessions for parents and children, providing social skills training and education about FASD	Improved parent knowledge about FASD; for children, greater social skills knowledge, improvement in social skills, and decrease in problem behaviors following intervention
Parents and Children Together (PACT), Children's Research Triangle, Chicago, IL	12-week program of weekly neurocognitive habilitation group therapy sessions; concurrent parent education group	Improved executive functioning and self-regulation skills amongst children
Families Moving Forward (FMF), University of Washington, Seattle	In-home training program (16 sessions over 9–11 months) providing education and support to families	Improved caregiver comfort and knowledge about FASD; improved problem behaviors
Parent-Child Interaction Therapy, University of Oklahoma	14-week program in which caregivers are provided with live, coached practice of parenting skills	Improved problem behaviors in children and decreased parent stress

Abbreviation: FASD, fetal alcohol spectrum disorder.

American Academy of Pediatrics FASD Expert Panel. *Fetal Alcohol Spectrum Disorders Toolkit.* http://www.aap.org/fasd. Accessed April 5, 2017; Senturias Y, Burns B. Managing children and adolescents with fetal alcohol spectrum disorders in the medical home. *Curr Prob Pediatr Adolesc Health Care.* 2014;44(4):96–101; and Bertrand J, Floyd RL, Weber MK, et al. *Fetal Alcohol Syndrome: Guidelines for Referral and Diagnosis.* Atlanta, GA: Centers for Disease Control and Prevention, 2004.

- No pharmaceutical interventions directly alter CNS abnormalities in children with FASD, but specific medications may be indicated for coexisting psychiatric or neurologic diagnoses.

WHEN TO ADMIT

- Typical management does not require admission to a medical or psychiatric hospital.
- Indications for admission include
  - Symptoms related to any of the mental health or behavioral conditions that could coexist with FASD
  - Refractory seizures or initial seizure workup and management
  - Evaluation of severe growth failure

WHEN TO REFER

- Diagnostic evaluation (if the patient does not meet strict criteria for FASD or if an alternate genetic diagnosis is suspected)
- Neurologic evaluation (if focal neurologic signs or seizure disorder are present or suspected)
- Neuropsychological or other developmental testing
- Significant social and family issues
- Nutrition evaluation (if significant growth disturbance)
- Pharmacologic management of coexisting psychological disorders

COMPLICATIONS

- Depending on the specific neurobehavioral profile of the individual with FASD, there can be considerable risks for secondary disabilities.
  - Mental health disorders
  - Disrupted school experiences (eg, suspensions, expulsions, dropouts)
  - Substance abuse
  - Involvement with the legal system (eg, arrests, incarceration)

REFERENCE

1. Adapted from Bertrand J, Floyd RL, Weber MK, et al. *Fetal Alcohol Syndrome: Guidelines for Referral and Diagnosis.* Atlanta, GA: Centers for Disease Control and Prevention, 2004; Hoyme HE, May PA, Kalberg WO, et al. A practical approach to diagnosis of fetal alcohol spectrum disorders: clarification of the 1996 Institute of Medicine criteria. *Pediatrics.* 2005;115(1): 39–47; and Senturias Y, Asamoah A. Fetal alcohol spectrum disorders: guidance for recognition, diagnosis, differential diagnosis, and referral. *Curr Probl Pediatr Adolesc Health Care.* 2014;44(4):88–95

DEFINITION

- General definition: an increase in body temperature.
- More accurately described as a homeostatic response under control of thermoregulation.
  - Distinct from hyperthermia: an increase in body temperature from conditions that overwhelm normal thermoregulation
- Normal core body temperature measured rectally ranges from 36.1°C–37.8°C (97°F–100°F), although, on rare occasions, it may be as low as 35.3°C (95.5°F) or as high as 38.3°C (101°F).
  - "Normal" temperature of 37.0°C (98.6°F) was derived from an 1868 study of >1 million axillary temperatures taken in adults.
    - This value may have no relevance for children, not only because adults were studied but also because axillary and rectal (core) temperatures correlate poorly.
    - Young children appear to have higher core body temperatures than adults, with temperatures slightly higher than 37.8°C (100.0°F) occurring frequently in those <2 years.
- Upper limits of the reference range for a rectal temperature are
  - 38.0°C (100.4°F) for neonates <1 month
  - 38.1°C (100.6°F) in 1-month-olds
  - 38.2°C (100.8°F) in 2-month-olds
- The lowest body temperatures occur between 2:00 and 6:00 am, and the highest occur between 5:00 and 7:00 pm.
- A consensus panel has recommended the lower limit of fever be defined as a rectal temperature of 38.0°C (100.4°F).

HISTORY

- Because many evaluations of the febrile child take place over the telephone, the clinician must take a pertinent history, including
  - Patient age (the younger the child, the more thorough the evaluation)
  - Associated signs and symptoms
  - Exposure to illness in family or community
  - History of recent immunizations
  - History of any recurrent infections (eg, urinary tract infections [UTIs], streptococcal infections, otitis media)
  - Duration and height of the fever
    - A low-grade fever that is present for many days (signifying chronic or benign illness) usually does not need to be evaluated as urgently as a temperature of 41.0°C (106°F) that is present for a few hours (indicating potentially serious infectious disease).
    - The height of the fever is often not very reliable in distinguishing viral from bacterial illness or even serious from nonserious disease.
  - Time of year
    - Winter: respiratory syncytial virus (RSV) and influenza virus infections
    - Spring and fall: parainfluenza virus infections (the most common cause of croup)
    - Summer: enterovirus infections

PHYSICAL EXAMINATION

Findings on General Physical Examination

- Pronounced hypermetabolic state.
- Flushed cheeks.
- Unusual glitter in the eyes.
- Sleepiness and lethargy or exceptional alertness and excited demeanor (particularly 5- to 10-year-olds).
- Pulse increased by about 10–15 beats per 1°C of fever.
- Increased respiratory rate.
- Hot and dry skin ("burning up with fever").
  - Distal extremities may be cold and pale (vasoconstriction), obscuring an extremely high core body temperature.
- Shivering or sweating (mechanisms by which the body increases or decreases temperature).
  - Excessive sweating may cause dehydration, particularly with poor fluid intake.
- Dry mouth and lips from rapid mouth breathing and dehydration.
- Febrile seizure may occur if irritability of the central nervous system (CNS) increases.

Small Infant

- Signs and symptoms may be less obvious.
- Shivering does not occur in the first few months of life.
- Diaphoresis is less frequent than in the older child.
- Irritability, pallor, and anorexia may be the only suggestions of illness; carefully measure temperature if the parent mentions these signs.

Examine

- Respiratory tract
  - Tympanic membranes
    - — Otitis media
  - Pharynx
    - — Pharyngitis
  - Nose
    - — Discharge of sinusitis or viral upper respiratory tract infection
  - Lungs
    - — Evidence of pneumonia or bronchiolitis
- Eyes
  - Conjunctivitis as a clue to adenovirus, influenza, or RSV infection, conjunctivitis-otitis syndrome, or Kawasaki disease
- Skin
  - Typical viral exanthems (rubella, roseola, or chickenpox)
  - Erythema marginatum (rheumatic fever)
  - Rose spots (typhoid fever)
- Lymph nodes
  - Generalized lymphadenopathy
    - — Viral illnesses (eg, infectious mononucleosis, hepatitis, cytomegalovirus infection)
    - — Leukemia or lymphoma
  - Localized enlargement
    - — Skin infection
    - — Tumor
- Isolated cervical lymphadenopathy
  - — Tuberculosis
  - — Cat-scratch disease (*Bartonella* infection)
- Musculoskeletal system
  - Localized bone tenderness (osteomyelitis)
  - Restricted range of motion in a warm joint (arthritis)
- Heart
  - Carditis of rheumatic fever
  - Infective endocarditis
- Spine
  - Diskitis.
  - Costovertebral angle tenderness should prompt examination of the urine for evidence of UTI.

Factitious Fever

- Pulse that is not correlated with the increase in temperature
- Inability to document fever when temperature is measured rectally
- Absence of sweating during defervescence

DIFFERENTIAL DIAGNOSIS

General

- Differentiate fever from hyperthermia, an increased body temperature resulting from conditions that overwhelm the normal process of thermoregulation.
  - Dehydration
  - Excessive muscle activity
  - Heat exposure
- Conditions associated with fever include
  - Infection
    - — If pulse rate is less than expected for the degree of fever, consider typhoid fever, tularemia, mycoplasma infection, or factitious fever.
  - Autoimmune disease
  - Neoplastic disease
  - Metabolic disease (eg, hyperthyroidism)
  - Chronic inflammatory disease
  - Hematologic disease (eg, sickle cell disease, transfusion reaction)
  - Drug fever and immunization reaction
  - Poisoning (eg, aspirin, atropine)
  - CNS abnormalities
  - Factitious fever
- Although any disease in these categories may cause fever at any age, some diseases are more likely to occur at some ages than at others.

Viral Infections

- Use findings of viral infections and their course to distinguish them from bacterial diseases.
- Viral infections tend to be less serious than bacterial infections.
  - Enterovirus
  - Influenza virus
  - Parainfluenza virus
  - RSV
  - Adenovirus
  - Rhinovirus
  - Rotavirus
- Herpes simplex virus (HSV-1/HSV-2) infection, especially meningoencephalitis, should be considered in any neonate who has risk factors (eg, maternal primary HSV infection, prolonged rupture of membranes, fetal scalp electrode use) or clinical evidence (eg, temperature elevation/depression or instability, seizures, lethargy, skin/oral/ocular vesicles, cerebrospinal fluid [CSF] pleocytosis, hemorrhage).

Bacterial Infections

- More aggressive and more serious outcomes compared with viral infections
- May be especially devastating in younger children with immature immune systems
- Infection that remains localized in the older child may, in the infant and toddler, disseminate rapidly to
  - Blood (bacteremia)
  - Lungs (pneumonia)
  - Meninges (meningitis)
  - Bones (osteomyelitis)
  - Joints (arthritis)

Distinguishing Bacterial From Viral Infections

- In younger children
  - Difficult to recognize bacterial infection because children cannot verbalize complaints.
  - Physical signs and symptoms are more subtle and easily missed.
  - Serious bacterial disease is especially difficult to diagnose in children with no obvious focus of infection.
- Efforts to improve the ability to diagnose a serious bacterial infection focus on 3 areas.
  - History and physical examination
    - Neither height of fever nor degree of toxicity is a reliable predictor by itself of bacteremia or serious bacterial infection.
  - Laboratory data
  - Response to antipyretics
    - The most unhelpful criterion in distinguishing serious bacterial infection from more benign viral infection.
    - Children with a serious infection respond to antipyretics no differently from those whose illness is less significant.
- A combination of clinical and laboratory criteria seems to be more useful than single predictors to identify infants at low risk for bacterial infection.
  - The Rochester Criteria are the most well-known.
    - The infant appears generally well.
    - The infant has been previously healthy.
      - Born at term (≥37 weeks' gestation)
      - Did not receive perinatal antimicrobial therapy
      - Was not treated for unexplained hyperbilirubinemia
      - Had not received and was not receiving antimicrobial agents
      - Had not been previously hospitalized
      - Was not hospitalized longer than the mother
    - No evidence of skin, soft tissue, bone, joint, or ear infection.
    - Laboratory values.
      - Peripheral blood leukocyte count $5.0–15.0 \times 10^9$ cells/L (5,000–15,000/mm^3)
      - Absolute band form count $\leq 1.5 \times 10^9$ cells/L (≤1,500 cells/mm^3)
      - ≤10 leukocytes per high-power field (×40) on microscopic examination of a spun urine sediment
      - ≤5 leukocytes per high-power field (×40) on microscopic examination of a stool smear (only for infants with diarrhea)
  - Given the marked decrease in pneumococcal and *Haemophilus influenzae* type b (Hib) serious bacterial infections since the introduction of their vaccines, the likelihood of serious bacterial infection in infants and toddlers with high fever is even less than it was when the Rochester Criteria were formulated.
    - A fairly limited assessment may be more suitable at this time in appropriately vaccinated children.

Sepsis

- The children at greatest risk with fever are those presenting with severe sepsis or septic shock.
  - Mortality is as high as 8%–12%.
- Systemic inflammatory response syndrome (SIRS) is defined by the presence of ≥2 of the following conditions, one of which must be abnormal white blood cell (WBC) count or abnormal temperature:
  - Temperature abnormality
  - Tachycardia or bradycardia
  - Increased respiratory rate
  - Abnormal WBC count
- Sepsis: SIRS and evidence or suspicion of infection.
- Severe sepsis: sepsis *and*
  - Cardiovascular dysfunction *or*
  - Acute respiratory distress syndrome *or*
  - 2 other organ dysfunctions
- Septic shock: severe sepsis *and*
  - Cardiovascular dysfunction despite >40 mL fluid in 1 hour
  - Systolic hypotension *or*
  - Need for vasoactive drugs to keep blood pressure normal *or*

- 2 of the following conditions:
  - Capillary refill >5 seconds
  - Unexplained metabolic acidosis
  - Oliguria
  - Lactate >2× the upper limit of normal
  - >3°F between peripheral and core temperatures
- Fluid refractory shock: Cardiovascular dysfunction persists despite >60 mL fluid in 1 hour.
- Catecholamine refractory shock: Cardiovascular dysfunction persists despite >10 mcg/kg/min of dopamine or need for epinephrine/norepinephrine.

Seizure

- Most dramatic manifestation of fever in a child.
- Generalized tonic or tonic-clonic seizure, usually lasting <15 minutes and occurring within 24 hours of the onset of fever, may begin without warning.
- Most parents are not aware that fever was present.
- The primary care physician may be called immediately after the seizure has occurred or after transport to the emergency department.
  - The child is likely to be postictal and have a rectal temperature of 39.0°C–40.0°C (102°F–104°F).
  - Seizure may be the first sign of meningitis or encephalitis.

Psychosocial Factors

- A visit or telephone call for minimal fever and little evidence of disease should prompt thorough assessment of the psychosocial factors that may be contributing to parental concern.
- Answers to the following questions and others may clarify the situation:
  - Is the main concern about something else—a hidden agenda?
  - What knowledge about fever and disease does the caregiver have?
  - Has the caregiver had a previous traumatic experience with disease resulting in excessive anxiety?
  - Might the patient be a vulnerable child?
  - Is this family dysfunctional, in which minor illness cannot be dealt with or is used as a means to meet other needs?

Factitious Fever

- Infrequent but well-described entity.
- Children as young as 8 years have been known to increase the thermometer reading artificially by rubbing the mercury thermometer bulb on the sheets or by exposing it to warm liquids.

LABORATORY EVALUATION

- In newborns (≤4 days old) with fever, a full workup is indicated.
  - Complete blood cell count
  - Differential count
  - Urine analysis
  - Cultures of blood, urine, and CSF
- In an older infant who appears nontoxic and is at low risk for bacterial infection
  - CSF and blood culture may be avoided if
    - Good observation and follow-up can be made within 24 hours.
    - Antibiotics are not administered.
  - If antibiotics are to be administered, full workup, including blood and CSF cultures, should always be performed.
- For children who do not appear toxic
  - Consider obtaining a leukocyte count.
  - If the count is >15,000 leukocytes/mm^3, consider blood culture.
  - Obtaining a leukocyte count and blood culture at the same time is easiest, with the blood sent for culture only if the leukocyte count warrants doing so.
  - Procalcitonin and C-reactive protein blood levels might have better sensitivity and specificity than leukocyte count in predicting serious bacterial infection, but studies vary widely with respect to the best cutoff levels.
- Given the current lower incidence of pneumococcal disease, avoiding blood tests altogether might be more cost-effective and reasonable if the child
  - Has received ≥3 doses of the Hib and pneumococcal vaccines
  - Does not appear toxic
  - Has no obvious focus of infection
  - Has reliable health care professionals and excellent follow-up capabilities
- Urine culture for febrile
  - Boys <6 months
    - A more recent study suggests that the urine dipstick may be an adequate screen for ruling out a UTI, with a negative predictive value >98%.
  - Girls <12–24 months
- Rapid diagnostic viral testing.
  - Available for influenza A and B, RSV, and enterovirus.
  - Sensitivity and specificity vary, but a positive result may help decrease the number of other tests that need to be performed to rule out bacterial infection.

IMAGING

- Chest radiography
  - Generally necessary only if clinical symptoms or signs suggest pneumonia (eg, cough, tachypnea, dyspnea, rales, decreased breath sounds, dullness to percussion).
  - At least one study has suggested that as many as 20% of children with a temperature of ≥39.0°C (102.2°F) and a leukocyte count >20,000 cells/mm^3 have pneumonia on the chest radiograph, even in the absence of respiratory symptoms and signs.

DIAGNOSTIC PROCEDURES

- Lumbar puncture
  - The younger the child is, the more difficult it is to diagnose meningitis clinically (eg, meningismus, Kernig sign, Brudzinski sign).
    - <12 months: Strongly consider lumbar puncture because clinical signs of meningitis may be absent.
    - 12–18 months of age: Consider lumbar puncture.
    - >18 months: Lumbar puncture is not routinely warranted except in the presence of signs and symptoms suggestive of meningitis or other intracranial infection.
  - Antibiotic treatment can mask meningitis; consider lumbar puncture in a child with a febrile seizure who has received antibiotics.
  - Reexamination after a convulsive episode may help determine whether examination of the CSF is needed.

TREATMENT APPROACH

- Treatment of fever is less crucial than evaluation and treatment of underlying cause of the fever.
- Emphasize with parents their role in observation for signs and symptoms associated with serious disease.
- Sepsis.
  - Early recognition and aggressive, goal-directed therapy can decrease mortality significantly.
  - Antibiotics within an hour.
  - Early and rapid fluid administration (eg, 20 mL/kg boluses of crystalloid given over 5–10 minutes).
  - Early use of inotropic agents as appropriate to normalize physiology.

WHEN TO REFER

- Patients with prolonged fever may be referred for specialized further evaluation.

WHEN TO ADMIT

- If the child appears toxic (eg, lethargic or irritable, noninteractive, poor perfusion), consider
  - Hospitalization *and*
  - Further diagnostic tests to assess for serious bacterial infection.

Fever of Unknown Origin

DEFINITION

- *Fever of unknown origin* (FUO) is defined as ≥2 weeks of daily rectal temperature >38.3°C (101°F) with cause not determined by simple diagnostic tests, including
  - Complete history
  - Thorough physical examination
- Some experts say that 1 of the 2 weeks of fever should be documented in the hospital.

HISTORY

- Careful documentation of fever is necessary before diagnosing FUO.
  - *Day of fever* is defined as a 24-hour period in which a temperature >38.3°C (101°F) occurs at least once.
  - Thorough explanation of the reference range of core body temperature for age, with its diurnal variation, may help to exclude patients who are not truly febrile but who instead have a high typical body temperature.
  - Physician should instruct parents in the technique of taking a rectal temperature.
  - Circumstances that may affect body temperature must be recorded.
    - All medications taken
    - Activities in which the child has participated
    - Environmental temperature
- Information must be obtained about
  - Travel
  - Patient residence, if outside the United States
  - Animal exposure
  - Frequency of exposure to other persons who have common febrile illnesses
  - Previous illness
  - Hospitalizations
  - Medications
  - Family history of disease
  - Race and ethnicity
  - Precise course of the exhibiting symptoms
- Meticulous documentation of dates is especially important.
  - Family should record on a calendar the daily time and degree of the fever, along with associated symptoms.
  - For children >11–12 years, a separate interview should be conducted alone with the child to
    - Obtain the child's perspective on the illness.
    - Elicit information about subjects difficult to discuss in presence of parents.
      - School
      - Peer relationships
      - Family functioning
      - Sexual identity and activity
- Some inflammatory diseases have recognizable fever patterns (eg, double quotidian fever of systemic juvenile idiopathic arthritis).
  - Fever patterns (ie, remittent, intermittent, sustained) rarely are diagnostic of a specific disease.
  - Determine whether even 1 or 2 days of normal temperature are interspersed between days of fever.
    - Child may have a series of rapidly sequenced brief febrile illnesses, masquerading as a single febrile illness.
- Careful documentation of fever should also help exclude pseudo-FUO, characterized by[1]
  - Absence of documented, persistent fever
  - Lack of objective, abnormal physical findings
  - History of significant or near-fatal illness
  - Parental fear of malignant or crippling disease
  - Frequent environmental exposure to illness
  - Absence of persistent weight loss
  - Reference erythrocyte sedimentation rate (ESR) and platelet count
  - Many missed school days because of subjective morning symptoms
  - Discordance of fever and pulse rate
  - Medical or paramedical family background
  - ≥1 of the following conditions:
    - Mild self-limited diseases
    - Behavioral problems
    - Parents who have misconceptions concerning health and disease
    - Families under stress
  - Child without a true fever if body temperature is measured accurately and consistently
    - Sometimes this must be done under hospital supervision.
- Periodic fever syndromes.
  - Some children have shorter-than-normal episodes of fevers that recur in a regular (periodic) fashion with predictable symptoms.
  - Many of these periodic fevers are now known to be genetically based and can be diagnosed by sophisticated genetic testing.

PHYSICAL EXAMINATION

- A full physical examination must be performed.
  - Rectal temperature
  - Respiratory rate
  - Heart rate
  - Blood pressure
- A discrepancy between heart rate and temperature suggests factitious fever.
- A thorough examination of the respiratory tract is indicated.
  - Inspection of the tongue and gums for aphthous ulcers
  - Inspection of the pharynx for hyperemia and exudate
  - Transillumination of the sinuses for sinusitis
  - Search for purulent nasal discharge
  - Auscultation of the chest for localized wheezing
- Inspection of the tympanic membranes for chronic otitis media.
- In the older child, examination of the teeth to exclude dental caries and periodontal disease.
- A new cardiac murmur may be a clue to rheumatic fever or infective endocarditis.
- Lymphadenopathy, especially if generalized, may suggest a viral infection.
  - Infectious mononucleosis
  - Cytomegalovirus
  - Toxoplasmosis
  - HIV
- If lymphadenopathy is limited to the cervical areas, the physician should consider periodic fever syndrome, Kawasaki disease, Kikuchi-Fujimoto disease (Kikuchi lymphadenitis), and cat-scratch disease.
- Joints must be examined meticulously for
  - Swelling
  - Restricted range of motion
  - Tenderness
- Skin rashes may suggest
  - Viral disease
  - Autoimmune disease, such as juvenile idiopathic arthritis
- Absence of sweating and presence of a smooth tongue are consistent with familial dysautonomia, a rare genetic disorder of thermoregulation.
- Imperative tests.
  - Rectal examination in the older child
    - Pararectal lymphadenopathy may suggest a pelvic infection.
  - Stool guaiac test
    - Positive result may be consistent with inflammatory bowel disease.

DIFFERENTIAL DIAGNOSIS[2]

Bacterial Infectious Diseases

- Bacterial endocarditis
- Bartonellosis (caused by *Bartonella henselae*)
  - Usually presents as classic cat-scratch disease; it may also manifest as atypical cat-scratch disease, producing prolonged fever and hepatosplenic abscesses, lymphadenopathy, or central nervous system disease.
  - If documented exposure to kittens and cats, serologic testing for *Bartonella* should be obtained; if positive result, an abdominal ultrasound should be considered.
- Brucellosis
- Chlamydia
  - Lymphogranuloma venereum
  - Psittacosis
- Dental infections
- Ehrlichiosis
- Leptospirosis
- Liver abscess
- Lyme disease (*Borrelia burgdorferi*)
- Mastoiditis (chronic)
- Mycoplasma infections
- Osteomyelitis
- Pelvic abscess
- Perinephric abscess
- Pyelonephritis
- Salmonellosis
- Sinusitis
- Subdiaphragmatic abscess
- Tuberculosis
- Tularemia

Viral Infectious Diseases

- Cytomegalovirus.
- Epstein-Barr virus (infectious mononucleosis) is the most common infectious cause of FUO.
- Hepatitis viruses.
- HIV and AIDS.
  - Assess the child for characteristic physical signs and symptoms and known risk factors.
    - Parental intravenous drug abuse
    - Parental sexual contact with individuals who may be HIV positive
    - HIV-positive mother
    - Hemophilia requiring transfusion of blood products
  - Fever is not usually the sole manifestation of HIV infection.

- HIV infection should be strongly considered and the appropriate laboratory tests performed if fever has been present for >2 months and is associated with ≥1 of the following conditions:
  - Failure to thrive or weight loss >10% from baseline
  - Hepatomegaly
  - Splenomegaly
  - Generalized lymphadenopathy (lymph nodes measuring ≥0.5 cm in ≥2 sites, with bilateral site involvement counting as one site)
  - Parotitis
  - Persistent or recurrent diarrhea
- Rickettsial diseases
  - Q fever
  - Rocky Mountain spotted fever

Fungal Infectious Diseases

- Blastomycosis (non-pulmonary)
- Histoplasmosis (disseminated)

Parasitic Infectious Diseases

- Malaria
- Toxoplasmosis
- Visceral larva migrans
- Visceral leishmaniasis

Autoimmune Diseases

- Systemic juvenile idiopathic arthritis
  - Fever is almost always associated with this illness.
    - Often precedes the joint manifestations by weeks or months.
  - The typical double-quotidian fever (2 fever spikes in 24 hours with a normal temperature in between) is a helpful clue.
- Polyarteritis nodosa
- Systemic lupus erythematosus
- Sarcoidosis

Malignancies

- Hodgkin disease.
- Leukemia (the most common malignancy in children).
- Lymphoma.
- Neuroblastoma.
- Pheochromocytoma.
- The reason for fever in these diseases is unclear.
  - May be related to endogenous pyrogen and other cytokines produced by the neoplastic cells

Periodic Fever Syndromes

- Recurrent fevers that do not satisfy the classic definition of FUO, associated with a well-defined constellation of symptoms.
- Many periodic fevers are now known to be genetically based and can be diagnosed by sophisticated genetic testing.
- PFAPA (**p**eriodic **f**ever, **a**phthous stomatitis, **p**haryngitis, and cervical **a**denopathy) is the most common.
  - Nonhereditary autoinflammatory syndrome.
  - Onset <3 years.
  - Sudden fever to 39.0°C–40.0°C (102°F–104°F) lasting 3–5 days.
  - Anorexia.
  - Mild oral ulcerations with pharyngitis, cervical lymphadenopathy, an increased leukocyte count, and an increased ESR.
  - Constellation of symptoms recurs every 3–6 weeks.
  - A single dose of corticosteroids may quickly resolve symptoms of individual episodes.
- Other periodic fever syndromes include
  - Cyclic neutropenia
  - Familial Mediterranean fever
  - Hyperimmunoglobulinemia D and periodic fever syndrome
  - Tumor necrosis factor receptor–associated periodic syndrome
- Periodic fever syndromes are found in various populations around the world and are associated with known genetic mutations.
  - The primary care physician should know the patient's race, ethnicity, and country of origin.
    - These factors may provide clues about a specific periodic fever syndrome.

Miscellaneous Causes

- Central diabetes insipidus
- Colitis, granulomatous
- Colitis, ulcerative
- Diabetes insipidus, central
- Diabetes insipidus, nephrogenic
- Drug fever
- Ectodermal dysplasia
- Familial dysautonomia
- Hemophagocytic lymphohistiocytosis
- Infantile cortical hyperostosis
- Kawasaki disease
- Kikuchi-Fujimoto disease
- Munchausen syndrome by proxy
- Nephrogenic diabetes insipidus

- Pancreatitis
- Pseudo-fever (factitious fever)
- Serum sickness
- Thyrotoxicosis

LABORATORY EVALUATION

- If history and physical examination disclose no specific findings and growth is within reference range, only simple diagnostic tests are indicated.
- Routine blood cell counts and urinalysis.
  - Not shown to be particularly useful; however, elimination from workup is not advocated.
- Purified protein derivative tuberculin skin test or interferon-gamma release assay.
  - Anergy may occur in active tuberculous infection.
- Blood, urine, and throat cultures.
  - Negative cultures exclude infections of these areas.
- ESR, C-reactive protein (CRP) level, and albumin/globulin ratio.
  - Most useful laboratory tests
  - Pursue further evaluation, particularly for an autoimmune disease or cancer, if
    - ESR is >30 mm/h *or*
    - CRP level is elevated *or*
    - Albumin/globulin ratio is inverted.
- The remainder of the evaluation should be individualized based on historical and clinical findings.
- Because infectious causes are the most common, specific serologic tests may be useful.
  - Hepatitis A and B
  - Epstein-Barr virus infection (infectious mononucleosis)
  - Bartonellosis
  - Toxoplasmosis
  - Cytomegalovirus
- Bone marrow examination.
  - Occasionally helps in diagnosis of
    - Tuberculosis
    - Leukemia
    - Metastatic cancer
    - Fungal infections
  - Should be considered only in children with
    - Clinical or laboratory suggestion of cancer *or*
    - Immunocompromised patients
- If ESR, CRP level, and albumin to globulin ratio are normal and no signs and symptoms are present that are specific to a particular disease, little can be gained from any of the previously discussed tests.
- Observation and periodic evaluation are the only measures required while the physician remains alert for the occurrence of new symptoms or signs.
- The physician must be ready to provide family members with a clear explanation of the evaluative process, reference results, and reassurance.

IMAGING

- Radiologic studies may be appropriate in certain individuals but should not be done routinely.
  - Sinuses
  - Gastrointestinal tract
  - Chest
- Radioactive gallium scan.
  - To detect occult abscesses and infections
  - Less useful in children than in adults
- Total-body computed tomography (CT).
  - May help find tumors
- Abdominal ultrasonography.
  - If abdomen is of primary concern
- With the advent of sophisticated imaging technology, an 18F-fluorodeoxyglucose positron emission tomography (PET) or PET/CT scan has been found especially helpful in diagnosing systemic onset idiopathic juvenile arthritis.
  - PET scans demonstrate areas of high glucose consumption, typically areas of tumor or inflammation.

TREATMENT APPROACH

- Fever without discernible cause is always difficult for clinicians because fever suggests disease.
  - Inability to identify the cause of fever can undermine the physician's credibility.
  - The longer fever persists, the more concern is raised by the parents.
- Intensive examination of all of the following is the physician's responsibility and first stage of managing the patient:
  - History
  - Physical examination
  - Social context of the child

WHEN TO REFER

- Referral to the following professionals may occasionally be necessary for additional assistance in determining diagnosis:
  - Pediatric infectious disease specialist
  - Rheumatologist
  - Specialized diagnostician
  - Any combination of these professionals

WHEN TO ADMIT

- Consider admission for
  - Patients in whom the accuracy of reported temperature is unclear or questionable; temperatures must be taken by hospital staff or under their direct supervision.
  - Patients who need multiple tests, many of which require procedural sedation.
    - — Coordinate these tests together over a period of 24–48 hours, if possible.

FOLLOW-UP

- The health care professional must continue to assess these children frequently to
  - Detect new findings early.
  - Maintain the confidence of the family while the fever continues.

PROGNOSIS

- Children with FUO generally do well, even though fever may last for weeks or months.

REFERENCES

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DEFINITION

- Terms used to describe leg and foot disorders
  - *Abduction:* deviation away from the midline of the body
  - *Adduction:* deviation toward the midline of the body
  - *Cavus:* medial longitudinal arch of the foot elevated
  - *Equinus:* foot plantar flexed, placing the toes below the level of the heel
  - *Femoral anteversion:* increased internal rotation or twisting of the femoral neck anteriorly relative to the femoral condyles
  - *Femoral retroversion:* extreme twisting of the femoral neck posteriorly relative to the femoral condyles
  - *Pes:* the foot
  - *Planus:* medial longitudinal arch of the foot flattened
  - *Talipes:* congenital deformity describing a foot twisted out of shape or positon
  - *Talipes calcaneus:* deformity of the foot in which the foot is dorsiflexed
  - *Torsion:* excessive or abnormal twisting along the long axis
    - *Internal torsion:* excessive or abnormal inward twisting
    - *External torsion:* excessive or abnormal outward twisting
  - *Varus:* medial or inward deviation of the distal segment of an extremity relative to the proximal (previous) segment
  - *Valgus:* lateral or outward deviation of the distal segment of an extremity relative to the proximal (previous) segment
  - *Version:* physiologic or normal twisting along the long axis
    - *Inversion:* physiologic or normal twist inward
    - *Eversion:* physiologic or normal twist outward
    - *Anteversion:* physiologic or normal twist forward
    - *Retroversion:* physiologic or normal twist backward

HISTORY

Rotational Deformities

- Metatarsus adductus
  - Possible maternal history of oligohydramnios, uterine fibroids, multiple gestation, or other cause of uterine crowding

Bowleg/Knock-knee

- Family history of metabolic, renal, or skeletal diseases
- Prior trauma or endocrine, metabolic, or bone abnormalities

Clubfoot

- May be associated with spina bifida, trisomy 18, or congenital amniotic band syndrome

Flatfoot

- Rigid flatfoot
  - If not congenital, there may be history of trauma, infection, arthritic process, or neuromuscular disease.

Pes Cavus

- Not seen at birth but develops in late childhood or later depending on underlying cause.
- Parents may note difference in the foot or begin to find it difficult to fit shoes properly.
- Seen in
  - Muscular dystrophy
  - Peripheral neuropathies
  - Disease of the spinal cord, brain stem, and cerebral cortex
- Neurologic conditions that may produce pes cavus as a late manifestation include
  - Cerebral palsy
  - Meningomyelocele
  - Poliomyelitis
  - Charcot-Marie-Tooth disease
  - Friedreich ataxia
- Family history should be sought because many conditions producing this deformity are inherited.

Toe Deformities

- Hallux valgus
  - Most cases are asymptomatic.
- Hammertoe
  - Mild cases cause no pain.
  - More severe cases can result in pain, corns, inflammation, and worsening contractures.
- Polydactyly
  - Family history in 30% of cases
  - Associated congenital anomalies include
    - Trisomy 13 and 21
    - Ellis-van Creveld syndrome (chondroectodermal dysplasia)
- Syndactyly
  - Family history often found

Toe Walking

- To identify cases with underlying pathology
  - Birth and developmental history and milestones
  - Stooling and bladder control

PHYSICAL EXAMINATION

- If a pathologic deformity of the legs or feet is diagnosed, the clinician should look for other congenital anomalies, especially those involving the skeletal system.

Rotational Deformities

- Intoeing.
- If the child's patellae are rotated inward ("kissing knees") while walking, the underlying problem is above the knee, most commonly femoral anteversion.
- If the patellae face straight forward, the underlying problem is below the knee, most commonly medial tibial torsion or metatarsus adductus.
- Less common causes include talipes equinovarus, metatarsus varus, and spasticity of internal rotator muscles of the hip, as in cerebral palsy.
- Excessive intoeing is likely to be caused by benign conditions representing variations of normal development from excessive rotations of the femur, tibia, or both.
- Intoeing does not usually cause pain or interfere with development or stability of gait.
- Out-toeing ("slew foot").
  - May be seen with
    - Excessive external tibial torsion and femoral retroversion
    - Posterior misdirection of the acetabulum, rigid flatfeet, and flaccid paralysis of internal rotator muscles of the hip
- Metatarsus adductus.
  - Graded by degree of adduction and flexibility of deformity.
  - Severity is graded by the heel bisector method.
    - Normally, a line bisecting heel and sole longitudinally lines up approximately with the second toe.
    - Mild if line falls through third toe.
    - Severe if between fourth and fifth toes.
  - Flexibility of the forefoot should be assessed.
    - With a flexible foot, the second toe can be easily brought in line with or past the heel bisector.
    - Defect more consistent with metatarsus varus or talipes varus if inflexible.
- Tibial torsion.
  - To assess tibial rotation, measure the thigh-foot angle, the axis of the foot relative to the axis of the thigh.
    - Infant or child is placed prone with knees together and bent to 90° with ankles in neutral position.
    - Acute angle made between axis of the femur and the heel bisector is the thigh-foot angle.
    - Internal or negative angle indicates internal rotation; external or positive angle indicates external rotation.
    - At birth, normal thigh-foot angle ranges from -35° to +40° with a mean of -5°.
    - In older children, average thigh-foot angle is +10° (+15° to +25° in adults).
- Femoral anteversion and retroversion.
  - Kissing knees, intoeing, clumsy gait, or preference for "W" sitting over lotus position.
  - Place child in prone position with knees flexed to 90°.
  - Lower leg is used as a pointer and legs are rotated through the axis of the hip joint.
  - If within reference range, the hip should move through ~50° of internal and 40° of external rotation.
  - In excessive femoral anteversion, there is increased internal rotation of the hip of ≥60°–65°, sometimes as much as 80°–90°, and decrease in external rotation to <20°.
  - In excessive femoral retroversion, there is increased external rotation and decreased internal rotation.
  - Until 1 or 2 years of age, clinical measurement using this method is limited by physiologic tightness of hip capsule.

Bowleg/Knock-knee

- Genu varum
  - Lay patient supine with ankles together and measure distance between knees to determine resolution over time.
- Genu valgum
  - Track by measuring distance between medial malleoli when child is standing with knees together.

Clubfoot

- The leg and its appended foot are turned to resemble a club.
  - Plantar flexion (equinus) of the ankle.
  - Adduction (varus) of the heel (hindfoot).
  - High arch (cavus) at the midfoot.

- Severe adduction of the forefoot.
- Foot cannot be passively manipulated into a normal position.

- Evaluation for associated neurologic, muscular, or other skeletal abnormalities should be performed.

Flatfoot

- Characterized by loss or absence of medial longitudinal arch when weight bearing
- Associated with
  - Pronated gait and stance
  - Eversion of calcaneus and valgus position of the heel
  - Prominence of the medial talar head
- Flexible flatfoot
  - Collapse of medial longitudinal arch and ankle pronation with valgus heel position are apparent when patient is standing.
  - Viewed from behind, Achilles tendon bends medially before arcing back laterally toward the everted calcaneus.
  - When patient stands on tiptoe, the medial longitudinal arch of the foot reappears.
- Rigid flatfoot
  - Arch remains flattened in weight-bearing and non–weight-bearing positions.
  - No return of normal arch when patient stands on tiptoe.

Pes Cavus

- A high-arched foot characterizes the deformity.
- Takes 1 of 2 forms.
  - Cavovarus, in which the calcaneus is inverted with tightness of the heel cord
  - Calcaneocavus, in which a high arch is present with normal heel alignment
    - Usually increased ankle dorsiflexion and plantar flexion of the forefoot caused by weakness of calf muscles

Toe Deformities

- Hallux valgus
  - Bursa forms from the constant irritation and inflammation, forming a painful bunion.
  - May see some degree of ankle pronation and flatfoot.
- Hammertoe
  - Contracture of proximal interphalangeal joint (PIP)
- Mallet toe
  - Callouses or nail deformities at the tip of the toe
- Claw toe
  - Involves all joints of the toe
    - Fixed hyperextension of the metatarsophalangeal (MTP) joints
    - Flexion at PIPs and distal interphalangeal joints
- Curly toe
  - Fourth or fifth toe is usually flexed downward and twisted underneath the adjacent toe.
- Polydactyly
  - 50% occur bilaterally.
  - 80% of extra digits are postaxial.
- Syndactyly
  - Interconnection between ≥2 toes
  - Varies from thin skin that partially connects digits to bony attachment (synostosis) between parts of the phalanges
- Bunionette (tailor bunion)
  - Occurs at the fifth MTP joint.
  - Bursa over the lateral aspect of the fifth MTP joint is prominent, inflamed, and painful.

Toe Walking

- Idiopathic toe walking
  - Child is able to place feet flat on the ground and have normal dorsiflexion but prefers toe-walking gait.
- To rule out underlying conditions
  - Leg-length discrepancies
  - Joint abnormalities
  - Limited range of motion
  - Neuromuscular examination for spasticity, abnormal bulk, tone, or sensation

DIFFERENTIAL DIAGNOSIS

Rotational Deformities

- Intoeing is generally caused by benign conditions.
  - Protective or compensatory shifting of body weight in pronation and knock-knee, both normal developmental stages
    - Most common cause of intoeing
    - Corrects itself in time
  - Developmental bowing
    - Self-correcting
    - May lead to temporary intoeing
  - Internal tibial torsion
  - Femoral anteversion
  - Metatarsus adductus
    - Talipes varus: Entire foot is inverted and forefoot is adducted.
    - Metatarsus varus: Forefoot is inverted and adducted; hindfoot and heel are in normal position.

  - — Clubfoot: Talipes varus and metatarsus varus have been considered lesser degrees of clubfoot.
  - Talipes equinovarus and metatarsus varus
  - Spasticity of the internal rotator muscles of the hip (seen in cerebral palsy)
  - Anterior misdirection of the acetabulum
- Out-toeing is seen with
  - Calcaneovalgus
  - Pes planovalgus
  - Flaccid paralysis of the internal rotator muscles of the hip
  - Posterior misdirection of the acetabulum
  - External tibial torsion

Bowleg/Knock-knee

- Genu varum (bowleg), when extreme or unilateral, may result from
  - Rickets
  - Chondroplasia
  - Osteogenesis imperfecta
  - Osteochondritis
  - Neuromuscular disorders
  - Blount disease (tibia vara)
  - Injury to the medial proximal epiphysis of the tibia
- Genu valgum (knock-knee)
  - Often associated with pronation.
  - More apt to be marked in children who are overweight.
  - Severe bilateral genu valgum caused by rickets, renal osteodystrophy, skeletal dysplasia.
  - Injury to the lateral proximal tibial epiphysis can cause unilateral genu valgum.

Clubfoot

- Severe metatarsus adductus
- Talipes varus
- Metatarsus varus
- Calcaneovalgus foot, characterized by eversion of the heel and forefoot, abduction of the forefoot, and dorsiflexion of the entire foot
  - Generally resolves in time with stretching exercises

Flatfoot

- Rigid flatfoot
  - Ankle pronation is generally significant.
  - In newborns, vertical talus and accessory tarsonavicular can be detected by presence of a bony prominence on the medial and plantar aspect of the foot and limitation of plantar flexion and inversion of the forefoot.
  - Tarsal coalitions are not usually detected until 13–16 years of age.
    - — Initially fibrous or cartilaginous bar connecting the hindfoot bones becomes ossified.
    - — Pain on walking.
    - — Pronated position with eversion of the forefoot.
    - — Peroneal tendons stand out prominently when inversion of the foot is attempted.
  - Calcaneonavicular coalition tends to develop between 9 and 13 years of age.

Toe Walking

- Differential diagnosis of bilateral toe walking includes
  - Spastic diplegia
  - Tethered cord
  - Diastematomyelia
  - Muscular dystrophy
- Unilateral toe walking.
  - Spastic hemiplegia
  - Congenitally short Achilles tendon
  - Shortened limb
  - Dislocated hip
  - Significant tibial bowing
- Other neuromuscular diseases.
- In males, hypertrophy of calf muscles and Gowers sign indicate Duchenne muscular dystrophy.

LABORATORY EVALUATION

- Extreme or unilateral genu valgum or genu varum
  - Targeted laboratory tests for underlying metabolic conditions

IMAGING

Rotational Deformities

- Intoeing and out-toeing rarely require imaging studies.
- Metatarsus adductus.
  - Necessary only when there is limited flexibility of forefoot to evaluate for talipes varus and metatarsus varus.
  - Placing the child in a standing position on a copy machine and taking a photocopy of the soles of the feet is an easy way to assess the heel bisector position.
    - — Allows for tracking progression or improvement over time

- Tibial torsion.
  - Computed tomography has been shown to be excellent for measuring exact degree of torsion; however, physical examination is generally sufficient.
- Femoral anteversion and retroversion.
  - Imaging required only with
    - Severe femoral anteversion
    - Late onset, severe, or worsening retroversion, possibly associated with hip disorders such as slipped capital femoral epiphysis

Bowleg/Knock-knee

- Extreme or unilateral genu valgum or genu varum
  - Radiographic examination to exclude rickets, chondroplasia, osteogenesis imperfecta, osteochondritis, Blount disease, injury to proximal epiphysis, or other pathologic process

Clubfoot

- Not generally required for diagnosis but useful to delineate pathologic findings and guide management

Flatfoot

- Flexible flatfoot does not require imaging.
- In rigid flatfoot, radiographs may be useful in identifying exact cause.

Pes Cavus

- Radiographic examination may be necessary if surgical management is under consideration.

Toe Walking

- Not indicated in most cases
- Neuroimaging if
  - Toe walking develops after a period of normal gait.
  - Underlying pathology is suggested by history or examination.

TREATMENT APPROACH

- Most problems require no treatment or are managed easily without consultations.
- A few require services of an orthopedist.

SPECIFIC TREATMENT

Rotational Deformities

- Intoeing/out-toeing.
- Most children will simply outgrow their variant.
- Metatarsus adductus.
  - Requires minimal, if any, treatment because resolves spontaneously, usually within the first year.
  - Parents may perform simple stretching exercises of the child's foot.
- Talipes varus and metatarsus varus.
  - Fixed deformities of the foot that require early referral and treatment.
  - Serial casting, long-leg splints that abduct the forefoot, or both.
  - Abduction stretching exercises and outflare shoes may be used as an adjunct but should not be the only therapy.
- Tibial torsion usually resolves on its own over time and treatment is usually not recommended.
  - Mainstay of treatment is parental reassurance and education about natural development.
  - Rarely, when severe residual internal or external tibial torsion affects function, surgery may be required.
    - Surgery should be delayed until at least 8–10 years of age.
- Femoral anteversion.
  - Most femoral torsion deformities self-correct by 7 years of age.
  - A simple measure if parents are concerned is to have the child learn to sit in the tailor, modified lotus, or cross-legged sitting position.
  - Use of splints is contraindicated.
  - Corrective shoes are of no value.
  - In rare cases, orthopedic intervention may involve bivalve lower trunk and leg cast or derotation osteotomy of middle or lower femoral shaft.

Bowleg/Knock-knee

- Simple observation and reassurance; the condition spontaneously corrects 99% of the time.
- When identified, the underlying causes of extreme varus or valgum deformities must be effectively treated to improve angulation.
- Treatment of severe bowing or knocking of the knees caused by underlying disease is determined by the nature of the condition and may include
  - Wedge osteotomy
  - Epiphyseal stapling
  - Nutritional, hormonal therapy
- Mild cases of Blount disease may be treated with bracing; more severe disease often requires surgery.

Clubfoot

- Serial casting may begin in first weeks of life and continue through several months.

- Recurrence.
  - Rate varies after manipulation alone.
  - Most common after casting within first 2–3 years but may happen as late as 5–7 years of age.
- Surgical correction (tenotomies, muscle transplantation, and arthrodeses) may be required in severe cases.
  - When conservative management fails *or*
  - Because of recurrence when the child is older.
  - Recurrence is much less likely after surgical correction, although functional outcomes are not necessarily better than with conservative measures.
- Early initiation of therapy will
  - Increase success rate of manipulative or conservative management.
  - Decrease the need for surgical intervention.

Flatfoot

- Treatment of flexible flatfoot remains controversial.
  - No treatment beyond parental reassurance is required if flatfoot is not causing problems.
  - Where the condition contributes to pain or impairs function, manage conservatively with arch support inserts.
  - Stretching may be beneficial in the case of tight Achilles tendons.
- Rigid flatfoot.
  - Treat underlying disease where it is the cause.
  - Treatment in most cases is with orthopedic shoes.
  - Surgery in accessory tarsonavicular or tarsal coalition (in ~10% of cases, usually in adulthood).
  - Vertical talus usually requires surgical correction early in infancy.

Pes Cavus

- Exercises to strengthen affected muscles.
- Metatarsal pads on inner soles of shoes or metatarsal bars on outer soles.
- Surgical correction may be required if contractures develop.

Toe Deformities

- Hallux valgus
  - Patients should wear shoes with plenty of toe room and avoid high heels.
  - If flatfoot is present, a shoe insert to correct the foot pronation may help prevent progression of the disease.
  - In more severe cases, surgical correction may be needed.
- Hammertoe
  - May be left alone in mild cases with no pain.
  - The child should have roomy shoes that allow the toes to stretch.
  - In severe cases, surgical correction may be needed.
- Mallet toe
  - Most cases are mild and need no treatment.
  - If a corn develops over the deformity, shaving and padding will help.
  - In more severe cases, surgical correction can be performed.
- Curly toe
  - If asymptomatic, curly toe requires no treatment.
  - Surgical transfer of the toe flexor is performed when condition is severe and causes irritation with shoe wear.
- Polydactyly
  - If the extra toe is not causing problems with walking and shoe wear, no treatment is needed.
  - Surgical excision of fully formed digits is generally performed after 9–12 months of age.
  - Suture ligation may be used at birth to remove vestigial digits.
- Syndactyly
  - Does not require treatment
- Bunionette
  - If padding does not help relieve discomfort, surgical correction is needed.

Toe Walking

- The only treatment required for idiopathic toe walking is reassurance.
- If it persists beyond 2–3 years of age, stretching exercises or a dorsiflexion-assist ankle-foot orthosis may be of benefit.
- Older children who develop mild Achilles tendon contractures may require serial casting.
- Any underlying pathologic cause should be treated with orthoses or casting as appropriate.

WHEN TO REFER

- Intoeing and out-toeing
  - Severe intoeing
  - Unsteady gait (especially while running) that causes stumbling
  - Condition that does not follow expected physiologic progression and growth

- Metatarsus adductus and metatarsus varus
  - Forefoot with limited flexibility
  - Condition that appears to be progressing or is not improving with growth
- Tibial torsion
  - Extreme rotation (especially when associated with difficulty walking or running)
  - Significant asymmetry
  - Sudden proximal tibial deviation
  - Condition that does not follow the typical pattern of improvement with growth
- Femoral anteversion
  - Extreme rotation (especially when associated with difficulty walking or running)
  - Significant asymmetry of the femoral anteversion
  - Condition that does not follow the typical pattern of improvement with growth
  - New-onset femoral retroversion
- Bowleg/knock-knee
  - Severe, asymmetric, or unilateral genu varum or genu valgus
  - Condition that does not follow the expected physiologic progression with growth
- Clubfoot
  - Immediate referral to an orthopedist on diagnosis of clubfoot
- Flatfoot
  - Presence of a rigid flatfoot
  - Symptoms not relieved through conservative management
- Pes cavus
  - Referral for evaluation by a neurologist, physiatrist, or orthopedist, individually or in collaboration
- Toe anomalies
  - Referral to a podiatrist or orthopedist if the anomaly leads to pain, uncomfortable shoe wear or ambulation, and if these symptoms do not respond to conservative management
- Toe walking
  - Persisting >3–4 years of age
  - Abnormal neuromuscular examination
  - Leg-length discrepancy of >1 cm or other significant physical abnormality on examination

FOLLOW-UP

- Many foot and leg problems are benign and resolve with time.
  - Close follow-up and monitoring for the resolution of condition is necessary.
  - If the condition does not resolve at the expected time, a referral to a specialist should be made.

PROGNOSIS

- Many common foot and leg problems are benign and resolve with time.

PREVENTION

- Shoes have 2 functions.
  - Protecting feet from trauma and extreme temperatures
    - Support to foot and ankle is a function of the shoe only when pathology is present.
  - Style
    - Style is the only reason for a baby to wear shoes before walking outdoors or being taken out in cold weather.
- First shoes for walking.
  - Hard-sole shoes may give some babies stability when first standing, but they have not been shown to enhance learning to walk.
  - Rigid shoes may prevent foot motion and diminish development of foot musculature.
  - Recommend properly fitting shoes with flexible, smooth soles and soft uppers.
- Determining the proper fitting for shoes involves no great science.
  - The foot widens while standing and throughout the day, so measurements should
    - Be made later in the day
    - Be made with the child standing
  - Both feet should be measured, and shoes should be fitted to the larger foot.
  - The counter should hug the heel snugly.
  - Length should allow a fingerbreadth (0.5") between the tip of the great toe and the toe box.
  - The foot should fit snugly into the widest part of the shoe.
  - Width should not crowd the ball of the foot and should allow the toes to extend without wrinkling the upper.
  - While still in the store, the parents should have the child walk in the shoes to ensure comfort.
  - Shoes should not be expected to stretch to fit; if shoes do not fit, they should not be purchased.

- Shoes in good condition can be handed down from one child to another.
- The frequency with which shoes should be changed depends on
  - Rate of growth of feet.
  - Quality of shoes.
  - Degree of their use.
  - Parents can usually tell when shoes become too small (or rather, when feet become too large) without professional advice.
    - Toes are felt to press against the toe box.
    - Getting the shoes on or having the child keep them on is increasingly difficult.

Foreign Bodies of the Ear, Nose, Airway, and Esophagus

DEFINITION

- Foreign bodies of the ear, nose, and respiratory and digestive tracts are a common problem among children, particularly those <5 years.
- Children are at risk as soon as the pincer grasp is achieved around 9 months of age.

SIGNS AND SYMPTOMS

Foreign Bodies in the Ear

- Most common among children 2–4 years of age.
- Eliciting a history of placing an object in the ear canal is difficult.
  - Most children are reluctant to admit to this activity.
  - If insertion is not witnessed, the foreign body may go undetected for an extended period.
- Findings depend on
  - Depth of the foreign object within the external auditory canal
  - Nature and composition of the object
  - Duration in the canal
- Children may complain of or the following symptoms may be observed:
  - Ear pain
  - Discomfort
  - Bleeding
  - Discharge
  - Odor
  - Aural fullness
  - Hearing loss
  - Nausea
  - Vomiting
  - Coughing
  - Tearing
  - Dizziness
- Inert substances, such as plastic, that are not obstructing the canal and are not abutting the tympanic membrane may not cause symptoms.
- Insects tend to incite local irritation.
  - Discomfort
  - Erythema
  - Drainage
- Food may cause local inflammation.
  - Often leads to local pain and itching
- Objects that touch the tympanic membrane cause pain, particularly with movement of the drum or swallowing.
- If the entire canal is obstructed, hearing will likely be decreased.
- Button-sized alkaline batteries may leak battery alkali and cause a severe local tissue reaction or destruction.
  - Pain, swelling, or discharge.
  - Expeditious management prevents serious injury to the canal, tympanic membrane, or middle ear.
- When the history indicates a small foreign body that cannot be seen, it may be lodged anteriorly in the tympanic sulcus.
  - Instillation of water to fill the medial half of the external canal may act as a concave lens and allow visualization.
- Microscopic evaluation will aid in visualization if a patient has a small, narrow, or swollen external ear canal.

Foreign Bodies in the Nose

- Children will usually not admit to placing foreign bodies in the nose.
- Most common symptom is unilateral nasal discharge that may be foul smelling.
  - Unilateral nasal discharge in a young child should be considered evidence of a foreign body until proved otherwise.
- Epistaxis may be the presenting symptom.
- Anterior nasal cavities should be examined with a nasal speculum and suction.
  - Powerful illumination is important.
- When an alkaline disk battery is lodged in the nose, symptoms may be acute.
- Tissue damage can occur through 3 mechanisms.
  - Electrical burn
  - Liquefaction necrosis (from sodium hydroxide)
  - Pressure necrosis

Foreign Bodies in the Airway

- When an object is aspirated, it initially produces
  - Choking
  - Gagging
  - Coughing
  - Wheezing
- This may be followed by an asymptomatic interval during which little evidence remains to suggest the presence of a foreign body.
- Depending on the site of the foreign body in the airway, a patient may exhibit a spectrum of findings from an almost complete lack of symptoms to signs of complete airway obstruction.

- High index of suspicion and knowledge of possible presentation scenarios are the best insurance against missed or delayed diagnoses.
- Laryngeal foreign bodies.
  - Most likely to produce acute and dramatic presentation
  - Large objects that completely obstruct the airway cause
    - Stridor
    - High-pitched wheezing
    - Cough
    - Dysphonia
    - Aphonia
    - Cyanosis
  - Small objects that obstruct partially but allow adequate air exchange produce
    - Cough
    - Stridor
    - Hoarseness
    - Pain or discomfort
- Tracheal foreign bodies.
  - Usually associated with cough, some degree of stridor, or wheezing
  - May produce an audible slap as the object moves from the carina to the glottis with respiration
- Bronchial foreign bodies.
  - Usually cause wheezing or coughing if they are partly obstructing.
  - Are often misdiagnosed as asthma.
  - With complete obstruction of a bronchus, an initial asymptomatic period is followed by a post-obstructive pneumonitis or bronchiectasis.
  - Sharp objects, such as pins or tacks, may cause pain or hemoptysis.

Foreign Bodies of the Esophagus

- Highest incidence in children 14 months–6 years.
- History of foreign body ingestion is often not obtained.
- Most foreign bodies pass through the esophagus undetected.
- Swallowed or aspirated object can cause a respiratory emergency, no symptoms at all, or anything in between.
- Objects that do not pass freely initially stimulate the larynx and cause gagging and coughing.
- Subsequent symptoms depend on size, composition, and nature of the foreign body.
- In young children, the following symptoms are common:
  - Poor feeding
  - Refusal to eat or drink
  - Increased salivation
- When the esophagus is completely or almost completely obstructed
  - Choking
  - Vomiting
- Duration of obstruction can affect clinical presentation.
  - The longer a foreign object is present, the greater the tissue reaction and local inflammation will be.
  - In the later stages
    - Pain on swallowing
    - Airway compromise
    - Fever
    - Leukocytosis

DIFFERENTIAL DIAGNOSIS

- Differential diagnosis of foreign bodies in the nose includes
  - Suppurative rhinitis.
  - Adenoiditis.
  - Sinusitis.
  - Nasal or nasopharyngeal tumors.
  - Nasal polyps also may cause unilateral nasal discharge.
  - In a young child, cystic fibrosis must be ruled out.

IMAGING

- Nose
  - Radiography may be helpful if the object is radiopaque or has become calcified.
  - Incidental finding of a nasal foreign body on a routine dental radiograph examination has been reported.
  - In a review of children who had nasal foreign bodies, 28 of 71 (39%) radiographs demonstrated a foreign body.
  - US toy manufacturers are required by law to make toy parts radiopaque.
    - Those outside the United States do not have to conform to this regulation.
- Airway
  - For objects suspected of being lodged in the laryngeal inlet, high-kilovolt anteroposterior and lateral radiographs of the upper trachea or esophageal inlet should be obtained if the patient's condition permits.
  - Bronchial foreign bodies may be demonstrated by air trapping in the affected lung on a dynamic radiographic study.
    - Inspiratory-expiratory radiographs
    - Lateral decubitus radiographs
    - Videofluoroscopy

- Esophagus
  - Posteroanterior and lateral chest radiographs, in addition to neck radiographs, are diagnostic if the object is radiopaque.
  - If the foreign body is a coin, it will be oriented in a transverse position because the opening of the esophagus is widest in a transverse position.
  - Contrast studies can be used when a foreign body that does not show on routine radiographs is strongly suspected.
  - If the foreign body is lodged at the lower border of the cricopharyngeus muscle, it will be visualized at the level of the clavicles on chest radiograph.

DIAGNOSTIC PROCEDURES

- Direct visualization of the foreign body by endoscopy may be necessary when it is not visualized by imaging techniques.

TREATMENT APPROACH

- The severity of problems caused by a foreign body depends on site, composition, and duration of time in the body.
- Removal is not usually an emergency except
  - If the airway is compromised
  - If the object is a battery
- Removal should be attempted only if the following circumstances are available:
  - Appropriate sedation or anesthesia.
  - Proper instrumentation and illumination.
  - Skilled practitioner.
  - Otherwise, attempts to remove the foreign body may aggravate the problem and jeopardize the child's well-being.

SPECIFIC TREATMENTS

Foreign Bodies in the Ear

- Nonurgent situations
  - Nonreactive foreign bodies that do not occlude the external canal completely or impinge on the tympanic membrane do not present an emergency.
- Aural foreign bodies may be removed by
  - Irrigation
    - Gentle irrigation may be used on nonabsorbable substances.
      - Ensure that the tympanic membrane can be visualized.
      - Make sure it is intact and that there is no evidence of inflammation of the external canal.
    - 18-gauge catheter attached to a 10- to 20-mL syringe.
      - The pressure generated is well below the pressure required to burst a tympanic membrane.
    - Flow of fluid should be directed around the retained object.
      - Allow back pressure to force the object out of the canal.
    - Fluids should be warmed to avoid irritation of the labyrinths.
    - Food tends to swell when water is applied, making removal difficult.
  - Suction
    - Frazier tip suction
  - Instrumentation
    - Choice of instrument will depend on the shape and composition of the object.
      - Alligator forceps
      - Right-angle hook
    - Pass instrument beyond the object, hook it from behind, and pull it out gently.
    - Management of embedded earrings includes local anesthesia, with an incision for removal of the earring.
      - Oral and intravenous antibiotics are used to treat infection or cellulitis.
- Urgent situations
  - In older children who are cooperative
    - Local anesthetic injected with a small-gauge needle into the skin lining the external canal may allow complete removal of the foreign body and subsequent examination.
  - In younger children or for those who are uncooperative
    - General anesthesia may be necessary.
      - Preferable to traumatic removal if the child cannot cooperate or cannot be restrained adequately
    - Remove the foreign body immediately when
      - The tympanic membrane cannot be visualized.
      - Evidence exists of inflammation or injury to the external canal.
  - Expeditious removal is particularly important with an alkaline battery.
    - Tympanic membrane perforations have been reported within only 8 hours of entry.
    - Magnets may be helpful for removing metallic objects, such as batteries or metal beads.

- Insects
  - Kill before removal.
    - Instill water, mineral oil, or topical lidocaine into the external canal.
    - Extract the insect with suction or alligator forceps.

Foreign Bodies in the Nose

- Remove as quickly as possible, particularly in the case of an alkaline battery.
  - Can cause severe local inflammation, with tissue damage occurring within 1 hour of placement.
  - Saline irrigation should be avoided because it can cause tissue damage.
- Young children are averse to nasal instrumentation, and removing a nasal foreign body requires cooperation or restraint.
  - Sedation or general anesthesia may be needed.
  - Topical application of a vasoconstrictor agent (eg, oxymetazoline, phenylephrine) in conjunction with removal of secretions by a small suction tip aids visualization, particularly when the object is in the middle or posterior nasal cavity.
- Endoscope is recommended for visualization.
- Most items can be removed with grasping instruments (eg, straight forceps, mosquito clamps).
  - If foreign body is firm and flat or has an edge, it may be removed by using a nasal bayonet or Hartmann or alligator forceps.
  - A wire loop may be placed beyond a spherical object, which is then removed by pulling the loop forward.
- Other methods include suction, irrigation, and adhesives.
  - Soft, friable objects can usually be removed with a Frazier tip suction device.
  - A Fogarty or small Foley catheter may be used for removal.
    - Place the catheter beyond the foreign body into the posterior portion of the nasal cavity or nasopharynx.
    - Inflate with 2–3 mL of physiologic (normal) saline solution.
    - Draw the catheter gently forward and out of the nose, expelling the object.
    - Foreign object may be dislodged by pushing it posteriorly into the nasopharynx, which may lead to aspiration.
  - Nebulized adrenaline together with nose blowing has been reported to expel nasal foreign bodies successfully.
  - Using pepper to induce a sneeze while the uninvolved nostril is occluded or blowing in the child's mouth while the contralateral nostril is held shut is not suggested.
  - Resuscitator bag insufflation of the mouth with the patient in the Trendelenburg position has been described.
- After removal, local inflammation exhibited by bloody or purulent oozing may be controlled with
  - Saline nose drops
    - Sterile water should be used in place of saline if the foreign object is an alkaline battery.
  - Antibacterial ointment (eg, bacitracin, mupirocin)
- A foreign body that remains in the nose for a long time may become calcified and form a rhinolith.
  - Removal is often difficult and bloody.
- For the situation in which magnets are stuck to each other on both sides of the nasal septum, using 2 cardiac pacemaker magnets and 2 forceps to remove them has proved effective.
- Physicians should consider a second foreign body in the nose or elsewhere.

Foreign Bodies of the Airway

- Foreign bodies that completely obstruct the laryngeal inlet create a life-threatening emergency.
  - They should be expelled immediately by using the Heimlich maneuver (abdominal thrusts).
    - For infants <1 year, the American Academy of Pediatrics recommends 5 back blows in the head-down position followed by 5 chest thrusts in the supine position, in place of the Heimlich maneuver.
    - Blind finger sweeps are dangerous and should be avoided.
  - If the foreign body cannot be expelled, a large-bore needle or angiocatheter (14 gauge) should be inserted into the cricothyroid space to allow ventilation until the patient can be taken to the operating room.
  - Alternatively, emergency tracheotomy may be necessary.
- Partially obstructing laryngeal foreign bodies should be treated in a manner that prevents total obstruction of the airway.
  - Back blows and abdominal thrusts should not be used in these cases.
- Tracheal and bronchial foreign bodies should be removed by a physician specifically trained for the task.
  - Procedure requires controlled endoscopic removal in the operating room.

- It is not usually an emergency, and adequate preparations can be made.

Foreign Bodies of the Esophagus

- Usually do not require emergency intervention.
- Endoscopic removal under anesthesia by a trained expert remains the method of choice.
- Remove the object as soon as possible after proper evaluation and preparation.
  - If the child has eaten recently, allow an appropriate period before administering general anesthesia.
  - If the foreign body is corrosive (eg, alkaline button battery), it should be removed as soon as possible to prevent severe inflammation and potential perforation of the esophageal wall.
- Multiple magnets lodged in the hypopharynx or esophagus can rapidly cause pressure necrosis.
  - If there is no history of esophageal disease and no respiratory compromise, 12–24 hours of expectant management for spontaneous passage could be considered.
- Rigid esophagoscopy.
  - Optical forceps are passed through the central channel for retrieval.
    - Allows for direct visualization of the esophagus, mucosa, and foreign body
- Flexible endoscopy.
  - A variety of flexible graspers, forceps, baskets, and magnets can be passed through the instrument channel for retrieval.
  - Non-endoscopic techniques are not recommended.
    - Using catheters to remove the foreign body can lead to aspiration, airway obstruction, and death.

WHEN TO ADMIT

- Foreign bodies in the airway
  - If prolonged or difficult instrumentation of the airway occurred during removal of the foreign body
  - If postoperative edema develops
- Foreign bodies in the esophagus
  - If the object is sharp and irretrievable by endoscope

WHEN TO REFER

- If airway compromise exists
- Anytime a battery is involved
- If the child cannot be restrained adequately
- If an object cannot be removed
  - Ear
    - If the tympanic membrane cannot be visualized or perforation is suspected
    - If the object is touching the tympanic membrane
    - If the object is spherical or in the canal for >24 hours
    - If hearing loss, nystagmus, vertigo, central nervous system deficits, or deep-seated infection exists
  - Nose
    - If a rhinolith has formed
  - Airway
    - For tracheal and bronchial foreign bodies
  - Esophagus
    - For endoscopic removal if perforation is suspected

FOLLOW-UP

- Foreign bodies of the ear
  - Postextraction care
    - After any foreign body is removed, the external canal and tympanic membrane should be thoroughly inspected.
    - If the external auditory canal appears infected or irritated
      - Topical antibiotic otic drops with steroids may be instilled.
      - The affected ear should be protected from water until it has healed completely.

COMPLICATIONS

Foreign Bodies of the Ear

- Complications can be caused by
  - The foreign body
  - Traumatic removal
- Laceration or inflammation of the external canal
  - Usually not serious
  - Resolves with instillation of liquid analgesics and antibiotics
- Perforations of the tympanic membrane
  - Carefully inspect to ensure that a flap of the membrane has not folded into the middle ear, leading to a permanent perforation or a cholesteatoma.
  - The middle ear space can become contaminated, and otitis media can develop.

Foreign Bodies of the Nose

- Complications include
  - Epistaxis
  - Local infection
  - Inflammation
  - Nasal septal perforation
- Occasionally a scar band, or synechia, forms between the turbinate and septum.
  - Prevent synechia by placing a splint made of Gelfilm or Silastic over the raw, exposed area.
- Obstruction of a sinus ostium by a foreign object may lead to the development of sinusitis.
  - Typically causes pain and tenderness over the affected sinus.
  - Clouding and an air-fluid level will be observed on the radiograph.
  - Treatment includes oral antibiotics and nasal decongestant drops.
- Aspiration can be prevented in most cases by prompt and skilled removal.

Foreign Bodies of the Airway

- Abdominal and chest thrusts may damage intra-abdominal contents (eg, liver, spleen) and ribs.
  - Use only in cases of complete airway obstruction that would otherwise cause certain death.
- Conversion of a partial airway obstruction to a complete obstruction can be prevented by having retrieval by skilled personnel.
- Pneumonia was the most common complication in 127 cases of foreign body aspiration.
- A bronchial foreign body that remains in place for an extended period may cause air trapping and irreversible bronchiectatic changes distal to the obstruction.
- Prolonged or difficult instrumentation of the airway during removal of a foreign body can lead to laryngeal edema or injury, with obstructive symptoms.
  - May require intubation after surgery.
  - Postoperative edema can sometimes be prevented by using steroids during and after surgery.

Foreign Bodies of the Esophagus

- Perforation of the esophagus can result from
  - Endoscopic retrieval
  - The foreign body itself
- Endoscopic removal is particularly dangerous with objects lodged at the level of the aortic arch.
- If an esophageal tear is suspected, a radiographic Gastrografin swallow study will usually confirm or negate the suspicion.
- Retropharyngeal abscess has been reported as the most frequent complication of a sharp esophageal foreign body.
- Foreign bodies that have been in the esophagus for long periods can cause a stricture to develop.
  - A contrast study, computed tomography, or esophagoscopy should be performed to aid in the diagnosis.

PREVENTION

- During anticipatory guidance, parents and caregivers should be instructed not to
  - Leave small objects or inappropriate food where a young child can reach them.
  - Give small objects or inappropriate food to a young infant.

Fragile X Syndrome

DEFINITION

- X-linked genetic condition characterized by trinucleotide repeats in the fragile X mental retardation 1 gene (*FMR1*) that alter fragile X mental retardation protein expression.

SIGNS AND SYMPTOMS

- Early recognition of the fragile X syndrome in childhood is very difficult; therefore, physicians should have a high index of suspicion.
- Delayed diagnosis is a significant problem in early childhood.
- Predominant features seen in early childhood include
  - Delayed attainment of motor milestones
  - Hypotonia
  - Developmental delay (especially speech)
  - Unusual behaviors
  - Feeding problems
  - Gastroesophageal reflux
- Characteristic physical signs in adults (large head; long face; prominent forehead, chin, and ears; joint laxity; macroorchidism) usually do not develop before puberty.
- Behavior issues in early childhood include
  - Features consistent with attention-deficit/hyperactivity disorder (ADHD)
  - Obsessive or perseverative activity
  - Emotional lability
  - Hypersensitivity to stimuli
- Autism spectrum disorder and psychiatric comorbidities occur frequently.
- Other potential abnormalities are seen in the following areas:
  - Ophthalmologic (strabismus)
  - Orthopedic (joint laxity)
  - Cardiac (mitral valve prolapse)
  - Skin (excessive softness and smoothness)
  - Neurologic (seizures)
- Affected males typically have moderate intellectual disability, and affected females have mild intellectual disability.

DIFFERENTIAL DIAGNOSIS

- Concurrent microarray comparative genomic hybridization is recommended to examine for non–fragile X conditions.
- Adults in the family with signs or symptoms of primary ovarian insufficiency (POI) (onset of menopause <40 years) or tremor or ataxia (as seen in fragile X–associated tremor/ataxia syndrome [FXTAS]) should be referred for testing.

DIAGNOSTIC APPROACH

- Consider children with the following conditions for molecular testing, regardless of negative family history:
  - Delayed motor milestones
  - Developmental delay (especially speech)
  - Intellectual disability
  - Autistic-like and other behaviors
- A positive family history for intellectual disability (especially, but not exclusively, in males) is another strong indicator for testing.

LABORATORY FINDINGS

- Molecular fragile X testing typically analyzes the number of trinucleotide repeats in conjunction with Southern blot analysis and polymerase chain reaction.
  - 5–44 repeats is a normal value.
  - 45–54 repeats is an intermediate result usually without significance.
  - 55–200 repeats is seen in premutation carriers.
  - >200 repeats is found in affected individuals.
  - Females will have 2 alleles to be measured; males will have only 1 allele.
- Newer techniques are being developed that overcome some current limitations in testing.

IMAGING

- Neuroradiologic abnormalities.
  - Decreased cerebellar volume
  - Increased ventricular volume
  - Increased white matter hyperdensity
- Routine neuroradiologic studies are not recommended except as clinically indicated.

DIAGNOSTIC PROCEDURES

- Developmental and behavioral assessments aid supportive and therapeutic management.

TREATMENT APPROACH

- No specific treatment is available.
- For affected individuals, educational and behavioral interventions are indicated.
  - Occupational therapy
  - Physical therapy
  - Speech therapy
  - Anticipatory management
  - Special education
- Pharmacologic therapy should be
  - Individualized
  - Used to treat psychiatric presentations

- Considered an adjunct for treatment of variable behavioral challenges not responding to environmental and behavioral interventions
- Integrated behavioral and pharmacologic program under the guidance of an experienced developmental team may prove helpful.
- Standard medical care is recommended for any health-related problem.

WHEN TO REFER

- Delayed motor milestones
- Developmental delay, especially speech
- Abnormal behavior (non-isolated ADHD or autistic features)
- Typical physical features (craniofacial abnormalities [long face; prominent forehead, chin, and ears] and macroorchidism)
- Positive family history for intellectual disability, females with POI (menopause <40 years), or males with adult-onset tremor or ataxia

FOLLOW-UP

- Appropriate behavioral, pharmacologic, and special education interventions as indicated by the individual circumstances.
- Adults in the family should be aware of associated risks.

COMPLICATIONS

- Intellectual disability and behavioral problems are the predominant complications that need appropriate supportive and pharmacologic treatments.
- Family members should be counseled about possible POI (onset of menopause <40 years) or FXTAS (tremors or ataxia >50 years).

PROGNOSIS

- Patients will need significant educational and behavioral assistance.
- They will typically require custodial care as they make the transition to adulthood.
- Assessment of additional family members should be considered because the additional risks will affect the longitudinal care of the patient and family.

PREVENTION

- Population-wide neonatal screening is being investigated but is not currently available.
- Because fragile X syndrome is a genetic condition, close attention should be paid to a thorough examination of family history and to the possibility of recurrence within the family.
  - Genetic counseling to review recurrence risks and potential testing would be helpful.
  - Premutation carrier females are at risk for having affected males and females because of the expansion of the trinucleotide repeats in female meiosis.
  - Recurrence risk counseling is sufficiently complicated that referral to a medical geneticist or genetic counselor is indicated.

DEFINITION

- Gastroesophageal reflux (GER)
  - Normal physiologic process that entails relaxation of the lower esophageal sphincter (LES) independent of swallowing.
  - Allows gastric contents to pass into the esophagus.
  - Occurs transiently several times a day in healthy infants, children, and adults.
  - Generally unaccompanied by symptoms.
  - The terms "spitting up," "posseting," and "spilling" are considered equivalent to regurgitation, which is the most visible symptom of GER in infants.
- GER disease (GERD)
  - Troublesome symptoms or complications associated with GER.
  - Symptoms can be esophageal or extraesophageal and can be further characterized by findings of mucosal injury on upper endoscopy.
- GER and GERD can be associated with *vomiting,* which is defined as a forceful expulsion of gastric contents through a coordinated autonomic and voluntary motor response.
  - *Regurgitation* occurs when gastric contents enter into the oropharynx.
  - Vomiting and regurgitation can be further differentiated from rumination.
  - *Rumination:* Recently ingested food is effortlessly regurgitated into the mouth, masticated, and re-swallowed.

SIGNS AND SYMPTOMS

- Symptoms, many of which are troublesome, and signs of GER depend on the age of the patient.
- Clinical manifestations may be different as children get older and with the development of language.
- Infants.[1]
  - Common presenting symptoms include
    - Refusing to eat
    - Recurrent vomiting
    - Poor weight gain
    - Irritability
    - Sleep disturbance
    - Respiratory symptoms
  - Infant crying has also been presumed to be a symptom of discomfort from acid reflux, but no studies have shown correlation of crying with GER.
- Older children and adolescents.[1]
  - Common symptoms include
    - Abdominal pain, heartburn
    - Recurrent vomiting
    - Dysphagia
    - Recurrent pneumonia
    - Upper airway symptoms (eg, chronic cough, hoarse voice)
  - Adolescents are more likely to report heartburn or chest pain—symptoms similar to those in adults.
- Extra-esophageal symptoms may occur at any age.
  - Wheezing
  - Stridor
  - Dystonic neck posturing

Symptoms and Signs of GER[2]

- Symptoms
  - Recurrent regurgitation with/without vomiting
  - Weight loss or poor weight gain
  - Irritability in infants
  - Ruminative behavior
  - Heartburn or chest pain
  - Hematemesis
  - Dysphagia, odynophagia
  - Wheezing
  - Stridor
  - Cough
  - Hoarseness
- Signs
  - Esophagitis
  - Esophageal stricture
  - Barrett syndrome
  - Laryngeal or pharyngeal inflammation
  - Recurrent pneumonia
  - Anemia
  - Dental erosion
  - Feeding refusal
  - Dystonic neck posturing (Sandifer syndrome)
  - Apnea spells
  - Apparent life-threatening events (ALTEs)

History in the Child With Suspected GER/GERD[2]

- Little is known about the natural history of children and adolescents with symptoms of GER/GERD.
- The following information should be obtained:
  - Feeding history
    - Amount and frequency (overfeeding)
    - Primary source of dietary proteins
    - Preparation of formula

- Recent changes in feeding type or technique
- Position during feeding
- Behavior during feedings (choking, gagging, coughing, arching, discomfort, refusal)

- Pattern of vomiting
  - Frequency and amount
  - Pain
  - Forceful
  - Blood or bile
  - Associated symptoms (constipation, fever, lethargy, diarrhea)
  - Associated pattern of stooling
- Medical history
  - Stool frequency and consistency
  - Preterm birth
  - Growth and development
  - Past surgery, hospitalizations
  - Newborn screen results
  - Recurrent illness (croup, pneumonia, reactive airways)
  - Apnea
  - Previous weight and length/height gain
  - Other chronic conditions
  - Warning signals
    - Bilious vomiting
    - Gastrointestinal (GI) bleeding: hematemesis, hematochezia
    - Consistent forceful vomiting
    - Onset of vomiting after 6 months of life
    - Failure to thrive
    - Diarrhea
    - Constipation
    - Fever
    - Lethargy
    - Hepatosplenomegaly
    - Bulging fontanel
    - Macrocephaly, microcephaly
    - Seizures
    - Abdominal tenderness, distention
    - Documented or suspected genetic/metabolic disorders (eg, trisomy 21)
- Medications
  - Current, recent, prescription, nonprescription
- Family psychosocial history
  - Sources of stress
  - Parental drug use
  - Postpartum depression
- Family medical history
  - Significant illness
  - GI disorders
  - Atopy
- Growth chart
  - Length/height, weight, head circumference
  - Weight for length, body mass index

DIFFERENTIAL DIAGNOSIS

Conditions Similar to GER

- A variety of conditions have clinical features that resemble GER, including
  - Eosinophilic esophagitis
  - Food allergy
  - Achalasia
  - Cyclic vomiting
  - Pill esophagitis
  - Infectious esophagitis
  - Rumination disorder
- These conditions may be suspected on the basis of characteristic features in combination with diagnostic testing.
- A failure of symptoms to respond to standard medical therapy for acid reflux may also be an indication for alternative diagnoses.

Specific Conditions

Eosinophilic Esophagitis

- Occurs in young children, teenagers, and adults.
- Younger children may have symptoms suggestive of GERD, such as abdominal pain or food refusal.
- Dysphagia or esophageal food impaction is more commonly noted in older children.
- A personal or family history of allergic disease is found in 75% of cases.
- The diagnosis is suspected when white exudate, circular rings, or linear furrowing is seen during upper endoscopy.
- Establishing diagnosis depends on finding >15–20 eosinophils per high-power field on an esophageal mucosal biopsy.

Food Allergy

- Infants with intolerance to cow's milk protein experience regurgitation and vomiting indistinguishable from that associated with physiologic GER.
- Cow's milk protein is among the first and most common proteins in an infant's diet and, accordingly, is one of the most common causes of food allergy.
- The prevalence of infant sensitivity to intact milk and other protein in the diet has been reported to be as high as 17% in developed countries.

- Such sensitivities vary in severity of reactions, are most often related to non–immunoglobulin E mediated allergy, and may be temporally dissociated from ingestion and feeding times.
- Intact soy protein may also be associated with formula intolerance and vomiting.
- Several well-controlled rigorous trials support the use of hypoallergenic (extensively hydrolyzed or amino acid–based) formulas in formula-fed infants as well as withdrawal of cow's milk and eggs from the maternal diet in breastfed infants.
- Recent evidence has implicated vitamin D deficiency as a potential modifiable risk factor for food allergy, but guidelines around prevention and treatment in this respect have not been developed.

Achalasia

- A neurodegenerative motor disorder characterized by lack of peristalsis in the distal two-thirds of the esophagus, an elevated resting pressure in the distal esophagus, and failure of the LES to relax.
- Results in functional obstruction in the lower esophagus and accumulation of food in the esophagus.
- This condition is extremely rare in childhood, with an incidence of 0.11 per 10,000 children annually.
- Children may have weight loss; regurgitation of undigested food; halitosis; cough, especially when supine; or pneumonia.
- The most common feature on chest radiograph is absence of air in the stomach and an air-fluid level in the esophagus.
- Barium esophagram often reveals a symmetric narrowing in the distal esophagus with the appearance of a bird beak.
- In young children with achalasia, sphincter relaxation and occasional peristalsis may be present.
- Esophageal manometry is often diagnostic.

Cyclic Vomiting

- A functional, debilitating GI disorder characterized by
  - Bouts of intractable nausea
  - Vomiting lasting for hours
  - Lethargy and pallor
  - Periods of complete symptom relief
- Reported incidence rates range from 1.7%–2.7% of school-aged children.
- The disorder has been reported in a number of countries around the world.
- The exact pathogenesis of cyclic vomiting remains unknown, but it has been well linked to migraine and is considered centrally mediated.
- During episodes, patients may require hospitalization and supportive care.
- Bouts may be triggered spontaneously, by stress, or by menstruation.
- Strong family history of migraine.
- No diagnostic test or identifiable neurologic, metabolic, or other GI disease exists to explain the condition.
- Recent guidelines on cyclic vomiting from the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) and its European counterpart society clarify the diagnostic process.
  - Both guidelines emphasize the importance of excluding other possible conditions before diagnosing cyclic vomiting.
    - Identifiable metabolic diseases
    - Obstructive uropathy
    - Intracranial processes
- Differential diagnosis of vomiting.[2]
  - GI obstruction
    - Antral, duodenal web
    - Esophageal ring or web
    - Pyloric stenosis
    - Malrotation with intermittent volvulus
    - Intermittent intussusception
    - Intestinal duplication
    - Hirschsprung disease
    - Foreign body
    - Incarcerated hernia
  - Other GI disorders
    - Achalasia
    - Gastroparesis
    - Gastroenteritis
    - Peptic ulcer disease
    - GER
    - Eosinophilic esophagitis
    - Eosinophilic gastroenteropathy
    - Food allergy or intolerance
    - Inflammatory bowel disease
    - Pancreatitis
    - Appendicitis
  - Neurologic disorders
    - Hydrocephalus
    - Subdural hematoma
    - Intracranial hemorrhage
    - Intracranial mass
    - Abdominal migraine, cyclic vomiting syndrome
    - Chiari malformation

- Infection.
  - Sepsis
  - Meningitis
  - Urinary tract infection
  - Pneumonia
  - Otitis media
  - Hepatitis
- Metabolic or endocrine disorders.
  - Galactosemia
  - Hereditary fructose intolerance
  - Urea cycle defects
  - Amino and organic acidemia
  - Congenital adrenal hyperplasia
- Renal disorders.
  - Obstructive uropathy, ureteropelvic junction obstruction
  - Renal insufficiency
- Toxic agents.
  - Lead
  - Iron
  - Vitamin A or D
  - Medications (eg, ipecac, digoxin, theophylline)
- Cardiac disorders.
  - Congestive heart failure
  - Vascular ring
- Others.
  - Cannabinoid hyperemesis syndrome
  - Pediatric falsification disorder (Munchausen syndrome by proxy)
  - Child neglect or abuse
  - Self-induced vomiting
  - Autonomic dysfunction

Pill Esophagitis

- Occurs when a pill becomes lodged in the esophagus.
- Characterized by acute onset of severe mid-chest or substernal pain and dysphagia.
- Well described as culprits in this scenario (especially in adolescents who may swallow medications without adequate liquids) are
  - Antibiotic treatments for acne (eg, doxycycline, minocycline)
  - Nonsteroidal anti-inflammatory medications (eg, ibuprofen)
- Condition is suspected based on history.
- Endoscopy may not be necessary if symptoms improve with acid-suppression therapy or sucralfate.

Infectious Esophagitis

- Most infectious causes of esophagitis present with odynophagia and not dysphagia.
- Herpes simplex virus, cytomegalovirus, and fungal infections, such as candidiasis, may occur in immunocompetent and immunocompromised hosts.
- Upper endoscopy may be beneficial in making the diagnosis by histopathology and culture.

Rumination Disorder

- Characterized by regurgitation of food into the mouth with subsequent re-swallowing of the material.
- Repeated masticatory movements, swallowing air, and tensing abdominal musculature help distinguish rumination from effortless GERD.
- Rumination was previously thought to occur in neurologically compromised children but is now recognized as occurring in otherwise healthy children and adolescents.
- It may also be a sign of underlying psychological distress or psychiatric disorders.
- Treatment generally involves professional counseling and, occasionally, psychiatric medications.

DIAGNOSTIC APPROACH

- No single gold standard test or testing approach allows a definitive diagnosis of GER or GERD.
- Diagnosis of reflux disorders is generally based on a description of symptoms in the absence of alternative diagnoses.
- Many diagnostic modalities can be used in a thoughtful and serial manner to provide specific information about the cause and severity of acid reflux and to investigate for associated or alternative conditions.

IMAGING

- Scintigraphy.
  - Oral intake of radiolabeled technetium followed by scanning the esophagus, stomach, and lungs to detect radiolabeled colloid that has been refluxed or aspirated.
  - Gastric emptying time may be calculated for potential therapeutic intervention.
  - Techniques of performing this test are not standardized, and age-specific normative data are not available.
    - Their role in evaluating GERD in children is unclear at this time.
  - NASPGHAN guidelines do not recommend routine use of scintigraphy in evaluation of children with reflux disorders.

- Upper GI radiography.
  - Generally involves obtaining a series of fluoroscopic images of swallowed barium until the ligament of Treitz is visualized.
  - Should be used to delineate anatomy.
  - Do not obtain to evaluate GI function or to diagnose GER or GERD because the test is too brief to adequately rule out pathologic reflux.
  - The high frequency of nonpathologic reflux during the examination can encourage false-positive diagnoses.
- An upper GI series can be useful in the evaluation of vomiting to screen for possible anatomic abnormalities of the upper GI tract but does involve radiation exposure.
  - Observation of the reflux of a barium column into the esophagus does not correlate with the severity of GERD or the degree of esophageal mucosal inflammation in patients with reflux esophagitis.
- Radiation-sparing imaging may, therefore, be preferable.
  - In infants with bilious vomiting, an upper GI may be useful for evaluating for possible malrotation or duodenal web.
  - However, if persistent non-bilious vomiting in an infant has led to a suspicion of pyloric stenosis, pyloric ultrasound should be performed first and upper GI reserved for situations in which the results of the pyloric ultrasound are equivocal.

DIAGNOSTIC PROCEDURES

- Thoughtful and serial diagnostic procedures should
  - Document the presence of reflux or gastric contents in the esophagus.
  - Detect complications.
  - Establish a causal relationship between reflux and symptoms.
  - Evaluate the efficacy of therapies.
  - Exclude other conditions.
- Esophageal pH and impedance monitoring
  - Can be used independently or in combination to quantify acid and nonacid refluxate.
  - Esophageal pH is evaluated using a transnasally placed probe that records the number and duration of acid reflux episodes.
  - Multiple intraluminal electrical impedance measures changes in electrical resistance and conductance in the mucosa when a fluid bolus moves down the esophagus, and this resistance and conductance detects nonacid and acid reflux.
  - Esophageal pH and impedance monitoring should be performed for a clinically meaningful period (ie, 12–24 hours) with recording.
  - Percentage of total time during which esophageal pH is <4.0 (called the *reflux index*) is the most valid measure of reflux.
    - Reflux index ≥12% in infants <1 year and ≥6% in children >1 year is considered outside of reference range.
    - ≤95% of children with mucosal evidence of esophagitis have a reflux index outside reference range.
    - Only 50% of patients with a positive pH study have esophagitis; severity of esophagitis has not been found to correlate with the reflux index.
  - Mounting evidence over the past decade suggests that independent esophageal pH monitoring is of limited value in pediatric reflux disorders and that combined pH and multiple intraluminal impedance testing should be considered the standard.
  - Combined pH and multiple intraluminal impedance testing is best recognized as a way to detect temporal relationships between specific clinical symptoms and acid reflux, rather than an independent means of diagnosing.
- Endoscopy and esophageal biopsy
  - Endoscopy allows direct visualization of esophageal mucosa to determine presence and severity of injury from the reflux of gastric contents into the esophagus.
  - Esophageal biopsies should be performed to allow for the evaluation of microscopic anatomy.
  - Upper endoscopy with esophageal biopsy is useful to evaluate inflammation in the esophageal mucosa from GERD and to exclude other associated conditions with symptoms that can mimic GERD, such as eosinophilic esophagitis.
  - However, the diagnostic benefits of upper endoscopy and esophageal biopsy must be weighed against the minimal, but not negligible, procedural and sedation risks that have been well associated with its performance.
  - Endoscopy with esophageal biopsies may be indicated in children with suspected GERD who fail to respond to pharmacologic therapy or as part of the initial management if symptoms of poor weight gain, unexplained anemia or fecal occult blood, recurrent pneumonia, or hematemesis exist.

- It may also be helpful in the assessment of other causes of abdominal pain and vomiting in children.
  - Esophageal or antral webs
  - Crohn esophagitis
  - Peptic ulcer
  - *Helicobacter pylori* infection
  - Infectious esophagitis
- Erosive esophagitis is reported less often in infants and children with GERD than in adults with GERD.
- A normal endoscopic appearance of the esophageal mucosa in pediatric patients does not exclude histologic evidence of reflux.
- The true value of esophageal biopsy is to evaluate for conditions that may mimic the symptoms of GERD, such as eosinophilic esophagitis, infectious esophagitis, Crohn disease, or Barrett syndrome.
- NASPGHAN guidelines strongly recommend endoscopy and esophageal biopsy when indicated for the evaluation of GERD in children.

TREATMENT APPROACH

- Management of GER/GERD involves
  - Lifestyle modifications
  - Buffering agents
  - Acid suppression
  - Promoters of gastric emptying and motility
  - Surgical therapy
    - Reserved for children at risk for life-threatening complications of GERD

SPECIFIC TREATMENTS

Lifestyle Changes in Infants

- May involve a combination of feeding changes and positioning therapy.
- Potentially effective strategies include
  - Modifying maternal diet
  - Changing formulas
  - Reducing the feeding volume while increasing the frequency of feeds
- NASPGHAN guidelines emphasize that milk protein allergy can cause a clinical presentation that mimics GERD in infants.
- Breastfed infants.
  - Maternal elimination diet is recommended.
  - May benefit from a maternal diet that restricts cow's milk and eggs.
- Formula-fed infants.
  - In one study, GERD symptoms resolved in 24% of patients after a 2-week trial of changing to a protein hydrolysate formula thickened with 1 tbsp of rice cereal per ounce, limiting the volume of feeding to 120 kcal/kg per day, avoiding seated and supine positions, and avoiding environmental tobacco smoke.
  - Another feeding management strategy involves the use of thickened feeds.
    - Adding up to 1 tbsp of dry rice cereal per 1 oz of formula *or*
    - Changing to commercially thickened (added rice) formulas for infants who are not cow's milk protein intolerant
- Positioning.
  - Keeping infants with GERD in the completely upright position or even placing them prone may be beneficial.
  - Many recent studies with impedance and pH monitoring have confirmed older studies that used pH monitoring to show significantly less GER in infants in the flat prone position compared with the flat supine position.
  - Guidelines are unequivocal that the risk for sudden infant death syndrome (SIDS) in sleeping infants outweighs the benefits of prone positioning in the management of GERD.
  - Prone positioning should be considered acceptable only if the child is observed and >1 year with GER or GERD because the risk for SIDS is greatly decreased in older age groups.
  - Semisupine positioning, particularly in an infant carrier or car seat, may exacerbate GER and should be avoided when possible, especially after feeding.

Lifestyle Changes in Children and Adolescents

- Lifestyle changes that may benefit GERD in older children and adolescents are more akin to those for adults.
  - Weight loss in overweight patients
  - Cessation of smoking
  - Avoiding alcohol use
- Recommendations for conservatively managing GERD in older children and adolescents may involve dietary modification and positioning changes, such as elevating the head of the bed.
  - Effectiveness of positioning changes in older children has not been as well studied as in infants.

- Older children should avoid caffeine, chocolate, alcohol, and spicy foods as potential symptom triggers.
- NASPGHAN guidelines also point out that 3 independent studies have demonstrated decreased reflux episodes with postprandial chewing of sugarless gum.

Pharmacotherapeutic Agents

- Several different medications may be used to treat GERD in infants and children.

Acid Suppressants

- Withdrawal of cisapride from commercial availability in most countries, including the United States, has led to a disproportionate use of acid suppressants to manage children with GERD.
- Main classes of acid suppressants are antacids, histamine-2 receptor antagonists (H2RAs), and proton-pump inhibitors (PPIs).
- The principles of using these medications in the treatment of pediatric GERD are similar to those in adults, other than the need to prescribe weight-adjusted doses and to consider the form of the drug prescribed (ie, for ease of ingestion in infants and children).
- Dosage ranges for drugs commonly prescribed for pediatric GERD are listed in **Table 1.**
- Antacids.
  - Directly buffer gastric acid in the esophagus or stomach to reduce heartburn and ideally allow mucosal healing of esophagitis.
  - Limited historical evidence that the on-demand use of antacids can relieve symptoms in infants and children.
  - Generally seen as a benign approach to treating pediatric GERD but are not entirely without risk.
    - Several studies link aluminum-containing preparations with aluminum toxicity and its complications in children.
    - Milk-alkali syndrome (hypercalcemia, alkalosis, and renal failure) has been described in children receiving calcium-containing preparations.
  - According to NASPGHAN guidelines, chronic antacid therapy is generally not recommended for the treatment of GERD in children.
  - No surface agent is currently recommended as independent treatment for severe symptoms of GERD or erosive esophagitis in children.
- H2RAs.
  - Major class of medications that has completely revolutionized the treatment of GERD in children.
  - Decrease the secretion of acid by inhibiting the H2 receptor on the gastric parietal cell.
  - Little clinical difference between the various formulations of H2RAs.
  - Clinical trials in children show that cimetidine and nizatidine are superior to placebo for the treatment of erosive esophagitis in children.
  - Pharmacokinetic studies in school-aged children suggest that gastric pH begins to increase within 30 minutes of the administration of an H2RA and reaches peak plasma concentrations 2.5 hours after dosing.
  - Acid-inhibiting effects of H2RAs last for ~6 hours, so H2RAs are quite effective if administered 2 or 3 times a day.
  - Limitations include
    - Fairly rapid tachyphylaxis can develop within 6 weeks of the initiation of treatment, limiting potential for long-term use.
    - Less effective than PPIs in symptom relief and healing rates of erosive esophagitis.
    - Although most of these downsides have been demonstrated most clearly in adults, they are also thought to affect children.
    - Cimetidine has specifically been linked to an increased risk for liver disease and gynecomastia, and these associations may be generalizable to other H2RAs.
- PPIs.
  - Most potent class of acid suppressants by repeatedly demonstrating superior efficacy compared with H2RAs.
  - Decrease acid secretion by inhibiting H^+/K^+-ATPase in the gastric parietal cell canaliculus
  - Uniquely able to inhibit meal-induced acid secretion.
  - Capacity to maintain gastric pH >4 for a longer period than H2RAs.
  - These properties contribute to higher and faster healing rates for erosive esophagitis compared with H2RA therapy.
  - Unlike H2RAs, the acid suppression ability of PPIs does not appear to diminish with chronic use.
  - The timing of dosing most PPIs is important for maximum efficacy.
    - Educate patients to administer PPIs ideally ~30 minutes before meals.

Table 1. Pediatric Doses of Common Medications Prescribed for Gastroesophageal Reflux Disease

Medications	Doses	Formulations	FDA-Indicated Ages
Cimetidine	30–40 mg/kg/d, divided in 4 doses	Syrup	≥16 y
Ranitidine	5–10 mg/kg/d, divided in 2–3 doses	Peppermint-flavored syrup Effervescent tablet	1 mo–16 y
Famotidine	1 mg/kg/d, divided in 2 doses	Cherry-banana-mint–flavored oral suspension	1–16 y
Nizatidine	10 mg/kg/d, divided in 2 doses	Bubblegum-flavored solution	≥12 y
Omeprazole	1–3 mg/kg/d (can be single dose or divided in 2 doses) Should be administered 30 min before eating or on an empty stomach.	Sprinkle contents of capsule onto soft foods.	2–16 y
Lansoprazole	1–3 mg/kg/d (can be single dose or divided in 2 doses) Should be administered 30 min before eating or on an empty stomach.	Sprinkle contents of capsule onto soft foods or select juices. Administer capsule contents in juice through nasogastric tube. Strawberry-flavored disintegrating tablet Orally disintegrating tablet via oral syringe or nasogastric tube (≥8 French)	1–17 y
Esomeprazole	Variable by age from 1 mo to >12 y	Sprinkle contents of capsule onto soft foods. Administer capsule contents in juice through nasogastric tube.	1–17 y
Rabeprazole	20 mg daily	Oral tablet	12–17 y
Dexlansoprazole	30–60 mg daily	Oral tablet	No pediatric indication
Pantoprazole	40 mg daily (adult dose)	Oral tablet	No pediatric indication

Abbreviation: FDA, US Food and Drug Administration.

- The metabolism of PPIs differs in children compared with adults, with a trend toward a shorter half-life, necessitating a higher dose per kilogram to achieve a similar peak serum concentration and area under the curve.
- Fairly wide range of effective doses is evident in children.
  - Open-label study of omeprazole in children revealed that an effective dosage range was 0.7–3.3 mg/kg daily, based on improvement in clinical symptoms and results of esophageal pH monitoring.
  - Lansoprazole, 0.7–3.0 mg/kg daily, improved GERD symptoms and healed all cases of erosive esophagitis in the treatment of 1- to 12-year-olds with GERD.
- Other trials of PPI therapy support the efficacy of treatment for severe esophagitis and esophagitis refractory to H2RAs in children.
- PPIs are considered safe and generally well tolerated with relatively few side effects.
- For long-term use, published studies have reported PPI use for ≤11 years in small numbers of children.
- The US Food and Drug Administration has approved several PPIs for use in children in recent years.
  - Omeprazole, lansoprazole, and esomeprazole for children ≥1 year
  - Rabeprazole for children and adolescents ≥12 years
- New guidelines describe a dramatic rise in the number of PPI prescriptions written for children, particularly infants, who may be at increased risk for lower respiratory tract infections.
  - Overuse or misuse of PPIs in infants with reflux is a matter for great concern.
- Limitations.
  - Placebo-controlled trials in infants have not demonstrated superiority of PPIs over placebo for reduction in irritability.
  - Headaches, diarrhea, constipation, and nausea have been described as occurring in ≤14% of older children and adults prescribed PPIs.
  - Although considered a benign histologic change, enterochromaffin cell hyperplasia was recently shown in ≤50% of children receiving PPIs for >2½ years.
  - Acid suppression in general with H2RAs or PPIs may be a risk factor for pediatric community-acquired pneumonia, gastroenteritis, candidemia, and necrotizing enterocolitis in preterm neonates.

Prokinetic Agents

- The desired pharmacologic effects include
  - Improving the contractility of the body of the esophagus
  - Increasing LES pressure
  - Increasing the rate of gastric emptying
- Efforts to design a prokinetic agent with benefits that outweigh deleterious side effects have proved difficult.
- Even metoclopramide, the most common prokinetic agent still available, recently received a black box warning about adverse side effects (11%–34% of patients), including drowsiness, restlessness, and extrapyramidal reactions.
- Although a meta-analysis of metoclopramide in patients <2 years with GERD confirmed a decrease in GERD symptoms, it was clearly at the cost of significant side effects.
- Other drugs in this category include bethanechol, cisapride, baclofen, and erythromycin.
  - Each works as a prokinetic by using a different mechanism.
- NASPGHAN guidelines unequivocally state that there is insufficient evidence to support the routine use of any prokinetic agent for the treatment of GERD in infants or older children.

Surgery as Management Strategy for GERD

- Several surgical procedures can be used to decrease GER disorders in children.
  - Fundoplication.
    - Gastric fundus is wrapped around the distal esophagus.
    - Most common.
    - Can prevent reflux by
      - Increasing the baseline pressure of the LES
      - Decreasing the number of transient LES relaxations
      - Increasing the length of the esophagus that is intra-abdominal to accentuate the angle of His and reduce a hiatal hernia, if indicated
  - Total esophagogastric dissociation.
    - Rarely used after failed fundoplication.

- Both procedures carry significant morbidity and do not reduce the risk for the direct aspiration of oral contents.

- Careful patient selection is one of the keys to successful outcome; candidates include
  - Children in whom pharmacologic treatments have failed
  - Children at direct life-threatening risk for aspiration of their gastric contents
- If acid suppression with PPIs is ineffective, the accuracy of the diagnosis of GERD should be reassessed because fundoplication may not produce optimal clinical results.
- Rule out clinical conditions such as cyclic vomiting, rumination, gastroparesis, and eosinophilic esophagitis; they are likely to still cause symptoms after surgery.
- If anti-reflux surgery is pursued, NASPGHAN guidelines stress the importance of providing families with adequate counseling and education before the procedure so they have a "realistic understanding of the potential complications... including symptom recurrence."

WHEN TO ADMIT

- Failure to thrive
- Aspiration pneumonia

WHEN TO REFER

- Failure of medical therapy
- Side effects of medical therapy
- Failure to thrive

COMPLICATIONS

Esophageal Complications

- GI bleeding associated with hematemesis, melena, guaiac-positive stools, or anemia can occur as a complication of GERD resulting from erosive esophagitis.
- Peptic strictures.
  - Long-known complication of severe GERD, especially in patients with neurologic impairment or esophageal motility disorders.
  - Children with peptic stricture may report dysphagia or refuse to eat solids.
  - Impaction of food may be the initial presentation.
  - Readily seen by barium swallow and usually located in the distal third of the esophagus.
- Barrett epithelium
  - Replacement of normal stratified esophageal epithelium with columnar epithelium and goblet cells.
  - Highly associated with peptic strictures in adults but rare in children.
  - May be premalignant.
  - Prevalence of esophageal cancer in children is extremely rare.
  - Children with Barrett syndrome should be managed according to adult guidelines and undergo appropriate surveillance for dysplasia.

Extra-esophageal Complications

- Chronic cough, stridor, hoarseness
  - Data are limited to case reports and case series.
  - Controlled studies of acid suppression to treat these presumed GERD-related symptoms have not shown clinical improvement.
  - Per NASPGHAN guidelines, do not assume patients with these symptoms have GERD without comprehensive evaluation for other potential causes.
- Recurrent pneumonia
  - Aspiration pneumonia and interstitial lung disease may occur without esophagitis.
  - Reflux causing recurrent pneumonia has been reported in otherwise healthy children.
  - Children with neurodevelopmental delay present a special diagnostic problem because oropharyngeal incoordination may result in aspiration without reflux.
  - Aspiration during swallowing in many patients (especially those with neurodevelopmental disorders) may be more common than aspiration of reflux material.
  - Diagnosing GERD as a factor in lung disease may be challenging.
  - Although lipid-laden alveolar macrophages have been considered an indicator of aspiration, multiple studies have shown poor sensitivity and specificity as an indicator of reflux-related lung disease.
- Asthma
  - Although symptoms of reflux are common in children with asthma and a high proportion of children with persistent asthma have abnormal pH monitoring, the relationship remains a challenge.
  - Esophageal acid exposure per se has minimal effect on pulmonary function.
  - Prevalence rates of GERD-associated asthma are reported to be 25%–75%.
  - ~50% of patients with persistent asthma who test positive for GERD by pH monitoring have no or minimal symptoms of GERD.

- In a clinical trial of asthmatic children 5–10 years of age, children with normal pH monitoring were randomized to receive a PPI or no acid-suppression treatment.
  - ~25% of asthmatic children with normal pH probe studies were able to decrease asthma medication, whereas children who were not treated with acid-suppression medication continued asthma therapy at the same dose.
- Studies have shown improvement of asthma symptoms after medical GERD therapies that included positional therapy, thickening of formula without medication, promotility agents, and an H2RA.
- Evidence is insufficient to establish optimal medical therapy for GER in children with asthma.
- The best test to determine whether an association exists between asthma and GERD is an empiric trial with a PPI for acid suppression.

■ ALTE
- An episode in an infant that requires intervention and is characterized by a combination of apnea, cyanosis, pallor, rubor, plethora, limpness, stiffness, choking, or gagging.
- Evidence to support a clear causal relationship between GERD and ALTE is lacking.
- In select cases, reflux may be associated with pathologic, central, and obstructive apnea.
- Medical therapy for GERD in infants with ALTE
  - Should be considered a reasonable therapeutic option to pursue.
  - Cannot be considered a reliable means of preventing a subsequent ALTE.
- Surgical therapy for GERD to prevent ALTE.
  - Unproven.
  - Should be considered only in infants with ALTE that is unresponsive to acid-suppression therapy and known to be associated with GERD.

■ Sandifer syndrome
- A rare complication of GERD usually seen in otherwise neurologically typical children
- Characterized by stereotypical, repetitive stretching and arching movements thought to be related to esophageal pain
- May be mistaken for atypical seizures or dystonia

■ Dental erosions
- An emerging association between GERD and dental erosions seems to correlate in severity to exposure of the proximal esophageal or oral cavity to acidic gastric contents.
- Young children and those with neurologic conditions may be at greatest risk.
- Beyond GERD, other contributing factors to dental erosions that can be considered causal or additive include juice drinking, bulimia, and genetic factors that affect the characteristics of the enamel and saliva.

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DEFINITION

- Food allergy is a common but often unsubstantiated diagnosis in pediatric practice.
- An adverse reaction to a food is any untoward reaction, regardless of its cause; it can be classified under 2 general categories.
  - Food allergy or hypersensitivity: an immunologic response
  - Food intolerance: a non-immunologic response caused by
    - Underlying congenital or acquired enzyme deficiency in which a specific dietary nutrient cannot be metabolized properly
      - Disaccharidase deficiency
      - Galactosemia
      - Hereditary fructose intolerance
    - Ingestion of a toxin (eg, *Staphylococcus*) in food
      - Shellfish
      - Mushrooms
    - Ingestion of a pharmacologic agent
      - Metabisulfite in wine or salad may cause bronchospasm.
      - Wine and monosodium glutamate may cause headache.
      - Caffeine may cause arrhythmia.
- Gastrointestinal (GI) allergic manifestations can be classified as
  - Immunoglobulin E (IgE)–mediated
    - Immediate GI hypersensitivity and oral allergy syndrome
  - Mixed GI allergy syndromes (involving some IgE components and some non–IgE- or T-cell–mediated components)
    - Eosinophilic esophagitis (EoE)
    - Eosinophilic gastroenteritis
      - These conditions share a common denominator: the response of the immune system to specific protein.
      - GI allergy can be divided into 2 types.
        - ▶ Specific allergy (self-limited, mainly T-cell–mediated condition that resolves in most by toddler age)
        - ▶ Eosinophilic or allergic GI disease with multiple food sensitivities (a more permanent condition)
  - T-cell–mediated allergic GI disorders (non-IgE mediated)
    - Dietary protein enteropathy
    - Protein-induced enterocolitis
    - Proctitis
- In all of these conditions, response of the immune system to a specific protein leads to pathologic inflammatory changes in the GI tract.
- Eosinophilic (or allergic) GI disorders (EGIDs) are characterized by infiltration of the GI tract with eosinophils.
  - Multiple food sensitivities are often identified.
  - Disorders are usually associated with other systemic allergies.
- EGIDs are subdivided into specific areas of the GI tract.
- New focus on EGIDs caused by increased research into EoE.

SIGNS AND SYMPTOMS

Cow's Milk Protein Allergy (CMPA)

- Systemic manifestations.
  - Anaphylaxis
  - Iron deficiency anemia (caused by GI blood loss)
  - Atopic dermatitis, urticaria
  - Peripheral eosinophilia
  - Poor sleep
- Respiratory manifestations.
  - Rhinitis
  - Wheezing
  - Pulmonary hemosiderosis
  - Nasopharyngeal obstruction leading to cor pulmonale
- GI manifestations.
  - Vomiting or gastroesophageal reflux (GER)
  - Diarrhea, malabsorption, protein-losing enteropathy
  - Enterocolitis
  - Constipation
  - GI bleeding
  - Failure to thrive
- The GI manifestations depend on the site of predominant inflammation in the GI tract.
  - Esophagitis causes recurrent vomiting and reflux.
  - Gastritis causes vomiting, irritability or pain, and occult GI bleeding.
    - Antral gastritis is a common finding, with increased eosinophils and inflammatory cells.
  - Enteritis causes diarrhea, malabsorption, or protein-losing enteropathy.
  - Colitis causes rectal bleeding, with blood or mucus in the stool.
  - A significant number of these infants experience straining or discomfort with stools.
  - Some infants can exhibit severe enterocolitis.

Soy Protein Allergy

- The clinical features of soy protein allergy are similar to those of CMPA, including
  - Esophagitis
  - Gastritis
  - Enteritis
  - Colitis
- Soy allergies are much less common than CMPA.
- Only 12% of all patients with CMPA will have concomitant allergy to soy protein.

Human Milk Allergy

- Breastfed infants may develop the same symptoms as those who are formula-fed.
  - Allergic colitis is the most common symptom.
  - Esophagitis.
  - Gastritis.
  - Enteritis.
  - Significant irritability.
  - Occult blood or obvious rectal bleeding.
  - Commonly asymptomatic.

EGID

- Diagnosis is based on clinical features as well as laboratory and radiographic findings.
- Disease manifestations of EGIDs depend on the depth of GI involvement.
- Mucosal disease (more common in children).
  - Dysphagia and heartburn, if limited to the esophagus
  - Vomiting, if involving the stomach
  - Protein-losing enteropathy, malabsorption, and diarrhea, if involving the small bowel
  - Bloody stools, if involving the colon
- Muscular disease (or submucosal).
  - Prominent inflammation in the stomach antrum can lead to pyloric obstruction.
- Serosal disease.
  - Causes eosinophilic ascites
  - Symptoms resembling peritonitis
- Patients with EoE have variable manifestations that may include
  - Feeding disorder.
  - Abdominal pain.
  - Vomiting.
  - Symptoms mimicking GER in young children.
    - — May have normal pH probe studies and fail to respond to antireflux medications
  - Symptoms may include dysphagia for solids or food impaction in older children.
- Other EGIDs have symptoms that vary with the anatomic site of eosinophilia and the depth of eosinophilic infiltration.
  - Mucosal form.
    - — Nausea, vomiting, colicky abdominal pain, diarrhea
    - — Occult blood loss, iron deficiency anemia
    - — Protein-losing enteropathy leading to hypoalbuminemia
    - — Failure to thrive/growth failure
  - Muscular (transmural) form.
    - — Obstructive symptoms, mimicking pyloric stenosis or thickening of the gastric outlet
  - Serosal form.
    - — Eosinophilic ascites
  - ~75% of affected patients have peripheral eosinophilia (with all 3 types).
- If the stomach is involved, patients may have evidence of delayed gastric emptying, including nausea and bloating or vomiting, a symptom suggestive of pyloric obstructive disease.

DIFFERENTIAL DIAGNOSIS

- CMPA
  - Other causes of rectal bleeding
    - — Rectal bleeding or guaiac-positive stools are probably the most common symptoms in infants with formula sensitivity.
    - — Allergy is the most common cause of rectal bleeding among infants <6 months.
  - Celiac disease
    - — Differentiation is made by the absence of anti-endomysial or anti–tissue transglutaminase antibodies in CMPA.
- EGIDs
  - Eosinophilia can be associated with
    - — Parasitic infestations
    - — Nutritional deficiencies
    - — Inflammatory bowel disease
    - — Neoplasms
- EoE
  - An evaluation to rule out reflux, typical eosinophilic infiltration of the esophagus on the biopsy specimen, and allergy testing.
  - Confirmation of food allergy is recommended, as 50%–90% of suspected food allergies are not substantiated.

DIAGNOSTIC APPROACH

- In patients with specific food allergies, removing specific food allergens from the diet ameliorates symptoms.
  - Reintroduction of the allergen leads to recurrence of symptoms.
- CMPA and soy protein allergy are the most clearly defined allergies in infants.
  - In patients with refractory reflux, food allergy, or formula sensitivity, these may coexist.
- CMPA.
  - GI symptoms predominate in many patients.
  - In others, anaphylaxis or pulmonary symptoms occur.
  - Infants with severe atopic dermatitis should also be evaluated for possible CMPA and other food allergy.
- EGID has no classic symptoms; it can go undetected for several years.
- Remains unclear whether these entities are variants of a similar disease process or distinctly different conditions.
- The diagnosis of EGID is based on clinical features and laboratory findings with confirmation by endoscopy.
  - Collaboration with a pediatric gastroenterologist is necessary.
  - A pediatric allergist can help direct specific testing for allergy.
- For EoE, diagnosis is based on
  - Patient or family history of allergy
  - Evaluation to rule out reflux
  - Typical eosinophilic infiltration of the esophagus on biopsy specimen
  - Allergy testing

LABORATORY FINDINGS

- In formula allergy, the infant may not have peripheral eosinophilia.
- IgE measurement and radioallergosorbent tests (RASTs) to detect IgE antibodies specific for milk and soy proteins.
  - Usually negative results, suggesting that immunologic mechanism occurs by means of a non-IgE (T-cell–mediated) mechanism.
  - Concomitant transient hypogammaglobulinemia or hypoalbuminemia caused by protein-losing enteropathy in a significant number of patients.
  - Treatment of the milk, soy, or other food allergy results in normalization of serum proteins.
  - Elevated IgE level or positive RAST result with these foods usually suggests long-term, rather than self-limited, sensitivity.
- EGIDs.
  - Half of patients have peripheral blood eosinophilia, elevated IgE levels, and an atopic history.
  - Hypereosinophilic syndromes are characterized by infiltration of many organs with eosinophils.
  - All EGIDs share a common feature of eosinophils infiltrating the GI tract, without involvement of extraintestinal organs.
  - EoE is the only EGID for which normal and abnormal eosinophil counts are established.
  - Because the mechanism of allergic GI diseases is probably on a spectrum between immediate hypersensitivity and cell-mediated immunity, the value of any single test is variable.
    - Allergy testing can include skin prick tests, RASTs, and patch testing.
    - Peripheral eosinophilia occurs, and an elevated IgE level is a variable finding; absence does not rule out EoE or other eosinophilic gastroenteropathies.
  - In other EGIDs
    - Laboratory studies may include hypoalbuminemia and low Ig levels caused by malabsorption and protein-losing enteropathy.
    - If the patient has long-term blood loss, laboratory studies may show iron deficiency anemia.

IMAGING

- EoE
  - Radiographic studies, including esophagography, may show thickened folds or a narrowing of the esophagus.
- Other EGIDs
  - Radiographic studies, including esophagography or upper GI tract study
    - May show thickened folds caused by edema in the esophagus or stomach.
    - May show gastric outlet obstruction.
    - Small-bowel follow-through may show nodular small bowel.

DIAGNOSTIC PROCEDURES

- Biopsy
  - The hallmark of GI biopsy results is an increased eosinophil count.
  - >20 eosinophils per high-power field on a rectal biopsy specimen is indicative of an allergic cause for colitis; however, any inflammatory lesion of the GI tract appears to attract eosinophils.
  - In CMPA, duodenal biopsy specimens reveal patchy changes, ranging from normal mucosa to flat gut lesions.
  - Although scattered eosinophils are normal throughout the rest of the GI tract, they are pathologic when seen in the esophagus.
    - Esophageal eosinophilia in reflux is mild (<15–20 eosinophils per high-power field) and is usually limited to the distal esophagus.
    - In EoE, eosinophilia is severe (>20 eosinophils per high-power field) and can involve most of the length of the esophagus.
  - If allergic gastroenteropathy involves the small bowel, the lesions are in a patchy distribution, ranging from areas of normal mucosa to a flat villus lesion.
    - Eosinophilic infiltration may be mild or marked.
    - Gastric abnormalities, found more commonly in the antrum, have been described as being consistent in the mucosal form of the disease.
    - The stomach shows evidence of gastritis, with destruction and regeneration of gastric glands and surface epithelium, and eosinophilic infiltration usually is marked.
  - In endoscopy of EoE
    - Mucosa may appear normal on gross examination.
    - Suggestive findings are often apparent, especially the classic ringed or furrowed esophagus and white exudates (seen exclusively in EoE).
  - Biopsy samples of EoE help quantify eosinophilic infiltration and inflammation if mucosal disease is present.
  - In other EGIDs, findings may be confusing because there is no consensus on histopathologic criteria.
    - The small intestine can reveal normal mucosa (with or without eosinophilic infiltration) and a flat villus lesion.
    - In the stomach, a gastric antral biopsy specimen is of diagnostic value in the mucosal form of the disease and is usually positive, revealing evidence of gastritis with marked eosinophilic infiltration.

TREATMENT APPROACH

- Treatment of food allergy includes primary prevention to prevent sensitization to proteins.

SPECIFIC TREATMENTS

Infant Formulas

- Once a specific protein allergy is suspected or diagnosed, the infant should initially be fed a hypoallergenic formula.
  - The choice of formula depends on the formula used at the time of diagnosis.
- Nonstandard infant formulas.
  - Soy protein with L-methionine.
    - Bright Beginnings Soy, Good Start Supreme Soy, Isomil Advance, Enfamil ProSobee
  - Partially hydrolyzed whey may help reduce the risk of CMPA but should not be used as treatment of existing allergy symptoms.
    - Good Start Supreme
  - Partially hydrolyzed casein, partially hydrolyzed whey.
    - Gentlease
  - Casein hydrolysate (hypoallergenic) if the patient is taking a milk-based or soy-based formula.
    - Alimentum, Nutramigen, Pregestimil
  - Amino acid base
    - Neocate, EleCare
- A comparison of partial versus extensive hydrolysates appears in **Table 1.**
- Allergy may last as little as 3–12 months; therefore, this period is one of trial and error as the patient is gradually retried on the previously proved allergen.
- ~10%–15% of infants given casein hydrolysate formula still have a persistent sensitivity, as evidenced by continual guaiac-positive stools or overt GI bleeding.
  - Many respond to the L-amino acid formulas, such as Neocate and EleCare.
  - These are expensive and should be used only when persistent sensitivity to all other formulas is well documented.

Table 1. Soy Versus Partial Versus Extensive Hydrolysates Versus L-Amino Acid Formulas

Category	Soy	Partially Hydrolyzed[a]	Extensively Hydrolyzed[b]	L-Amino Acid
Decreases protein sensitization	No	Yes	Yes	Yes
Treatment for established CMPA	No	No	Yes	Yes
Type of formula	Routine	Routine	Specialty	Specialty
Cost	Comparable with standard cow's milk formula	Comparable with standard cow's milk formula	3–4 times costlier than standard	Even more expensive than extensively hydrolyzed formula
Palatability	Comparable with standard	Comparable with standard	Less than standard	Less than standard formula

Abbreviation: CMPA, cow's milk protein allergy.

[a] Partially hydrolyzed whey

[b] Extensively hydrolyzed casein

- Milk or milk products from animals other than cows have been used anecdotally, eg, sheep's or goat's milk.
  - Risk of possible cross-reactivity between cow's milk proteins and sheep's or goat's milk proteins.
  - Goat's milk is folate deficient.
- In a prospective German study, there seems to be a slowing of body mass index gain in the first year of life for infants on extensively hydrolyzed formulas; no appreciable growth differences were noted when followed up to 10 years of age.

Human Milk Allergy

- Treatment in infants who are sensitive to mother's milk involves persuading mothers to avoid cow's milk products.
- Not all infants will respond to this measure.
  - Accidental maternal ingestion of milk proteins
  - Some other factor
- Inform mothers that most infants who show sensitivity to foods the mother is eating do not have severe disease and breastfeeding can be continued unless symptoms are significant.
- Mothers who exclude multiple foods from their diets should consider vitamin and calcium supplementation.
- Use of a hypoallergenic formula may be worth a trial to determine whether the infant's symptoms disappear.

EGID

- If foods test positive on a combination of tests for immediate or delayed hypersensitivity and food challenges, these foods should be eliminated from the diet.
- The most common foods implicated are, in order, milk, egg, soy, corn, and wheat.
  - Several foods may be found to cause symptoms.
- Dietary elimination of these allergens may alleviate most symptoms.
  - Some patients require complete dietary elimination with an L-amino acid–based formula.
  - An advantage of dietary management is a good rate of cure.
  - Restrictive diets may be difficult for children and may create social and behavioral problems.
  - Exclusive reliance on specialized formulas can be very expensive.
- For patients who cannot follow a restrictive diet, corticosteroid therapy may be required intermittently.
  - Quickly improves symptoms and normalizes tissue on biopsy specimens.
  - Steroids cannot be used on a long-term basis, and esophageal eosinophils and symptoms can recur after discontinuing therapy.

- Topical steroids, such as swallowed fluticasone propionate, improve symptoms and histologic findings.
  - Eradication of eosinophils in the esophagus is less consistent with topical therapy, and symptoms and baseline histologic values return on discontinuation.
  - Topical treatment is associated with esophageal candidiasis.

- Oral cromolyn sodium (Gastrochrom) has not been proven helpful.
- Leukotriene receptor antagonists improve symptoms but do not change histologic values.
- Symptomatic strictures resulting in food impactions or severe dysphagia may require endoscopic dilation.
- Pyloric obstructive disease may require surgery.
- If patients have other symptoms of allergy or atopy, these should be addressed as well.
- >50% of patients with EGID have a personal history of allergy, such as eczema, asthma, allergic rhinitis, or multiple food sensitivities.

WHEN TO ADMIT

- Anaphylaxis
- Severe malnutrition

WHEN TO REFER

- Poor weight gain
- Immediate GI response after particular food or foods
- Incomplete response to exclusion or elemental diet
- Multiple food allergies
- Multiple allergic symptoms
- Malabsorption or protein-losing enteropathy
- Gastroesophageal reflux disease recalcitrant to appropriate therapy
- Suspicion of EoE

COMPLICATIONS

- CMPA
  - Profuse vomiting or diarrhea can lead to shock, anemia, and methemoglobinemia.
  - Children with enterocolitis may be predisposed to a severe rare form of enterocolitis to solid-food antigens later in life.
    - They may develop severe reactions to food proteins considered to be of low allergenicity.

PROGNOSIS

- CMPA
  - Previously, physicians counseled families that infants with CMPA would outgrow it by 2 years of age.
  - Later studies revealed that allergy may persist in
    - 72% at age 2 years
    - 44% at age 4 years
    - 32% at age 6 years
  - Other studies are less pessimistic.
    - 44% with persistent symptoms at 1 year
    - 33% at 2 years
    - 23% at 3 years
  - Patients who have longer persistence of symptoms have
    - Symptoms later after initial introduction of milk
    - Higher frequency of allergic disease
    - Multiple food allergies
- EGID
  - Evidence indicates EGIDs are lifelong conditions with remissions and exacerbations, often requiring careful dietary manipulation and intermittent steroid therapy.
  - Preliminary data suggest younger adolescents go through a phase in which they are much better able to tolerate foods to which they were previously sensitive.
  - If the EGID produces significant malabsorption, osteoporosis may occur.
  - Natural history of EoE remains unclear.
    - Among adults with initial misdiagnoses of reflux, some develop strictures requiring dilation.
    - The esophagus can be friable, tearing with the mere passage of an endoscope.
    - Possible evolution to Barrett syndrome remains to be studied.

PREVENTION

- American Academy of Pediatrics 2008[1] recommendations for prevention of allergy
  - Nutritional interventions are largely limited to infants at high risk of developing allergy (ie, infants with ≥1 first-degree relative with allergic disease).
  - There is "evidence" that compared with intact cow's milk protein formula, exclusive breastfeeding for at least 4 months prevents or delays the occurrence of atopic dermatitis, cow's milk allergy, and wheezing.

- There is "modest evidence" that atopic disease may be delayed or prevented by the use of extensively or partially hydrolyzed formulas compared with intact cow's milk formula, particularly for atopic dermatitis.
- There is "little" or "no current convincing" evidence that the timing (delaying) of introduction of complementary foods beyond 4–6 months of age prevents the occurrence of atopic disease.
- There is "no convincing" evidence for the use of soy formula for allergy prevention.
- Current evidence does not support maternal dietary restrictions during pregnancy or lactation.

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DEFINITION

- Bleeding at any point along the length of the gastrointestinal (GI) tract, from the mouth to the anus.
  - Upper GI tract: proximal to the ligament of Treitz
  - Lower GI tract: distal to the ligament of Treitz
- Bleeding may be arterial, venous, or both.
- Terms describing specific characteristics of GI bleeding may give clues to nature, duration, and location of the bleed.
  - Hematemesis: bloody vomitus, usually representing bleeding proximal to the ligament of Treitz
    - Dark and coffee ground–like when altered by gastric acid
    - Bright red when little or no contact with gastric acid
  - Melena: black, tarry, sticky stools that result from hemoglobin denatured by intestinal bacteria and enzymes
    - From GI bleeding proximal to the ileocecal valve
  - Hematochezia: red, bloody stools
    - Usually results from distal GI bleeding.
    - Occasionally, rapid bleeding from an upper GI source along with the cathartic action of blood can speed transit time and result in hematochezia.

HISTORY

- The physician must quickly assess severity to expedite appropriate resuscitative measures.
- The physician must consider the most likely causes.
  - Does the problem require immediate surgery?
  - Does the problem require medical evaluation and management?
- The workup is based on
  - Patient's age and history
  - Patient's clinical appearance
  - Physician's familiarity with the patient
- A detailed history may help determine the location and duration of the bleeding.
- A family history of polyps, bleeding disorders, or GI diseases is important.
- Presence or absence of abdominal pain.
  - If present: location, severity, and quality
- Associated systemic symptoms (eg, with hemolytic uremic syndrome [HUS] or inflammatory bowel disease [IBD]).
- Altered mental status or lethargy.
- Suggestion of surgical cause (eg, Meckel diverticulum, intussusception, volvulus).
- Color of the stool.
- Description of emesis.
  - Whether a change has occurred in either in the preceding days or weeks
- Vomiting that progresses from bile-stained to bloody.
  - Intestinal obstruction (eg, volvulus, intussusception, necrotizing enterocolitis [NEC])
  - Mallory-Weiss tears
- Bloody diarrhea.
  - Infectious enteritis.
  - Food allergy.
  - IBD.
  - May precede HUS.
- Painless lower GI bleeding.
  - If substantial
    - Meckel diverticulum
    - GI vascular anomalies
  - If less severe
    - Polyps
    - Lymphonodular hyperplasia
- Fever.
  - Common in infectious or inflammatory disorders
- Arthritis and rash are seen with Henoch-Schönlein purpura (HSP).
- Neonatal history should focus on risk factors for NEC or varices.
  - Umbilical vein catheters
  - Liver disease
  - Birth asphyxia
- Sexual activity or abuse involving anal penetration should alert the clinician to anal and rectal trauma.

PHYSICAL EXAMINATION

- A complete and systematic examination should be performed because clues to the diagnosis may be present in any organ system.
- General appearance and vital signs can be helpful in determining duration of bleeding.
  - Acute GI bleeding may occur with or without signs of shock, depending on the amount of blood loss.
  - Slow, chronic bleeding allows time for physiologic changes.
    - Compensatory tachycardia
    - Orthostasis
    - Decreased pulse pressure
    - Fatigue
    - Pallor
- The nose and mouth should be examined for bleeding lesions or burns.

- The abdomen, perineum, and rectum should be thoroughly examined.
  - Abdominal examination to assess
    - Tenderness
    - Bowel sounds
    - Masses
    - Hepatosplenomegaly
    - Signs of chronic liver disease
      - Telangiectasias
      - Jaundice
      - Hepatosplenomegaly
      - Prominent abdominal venous pattern
- Rectal examination, with special attention to the perianal region.
  - Skin tags
  - Abscesses
  - Fissures
  - Bleeding points
  - Hemorrhoids (uncommon)
  - Character and color of stool
  - Occult blood on guaiac testing
  - Palpation for polyps and pelvic masses
- Digital rectal examination should follow in an attempt to discover
  - Anal fissures
  - Rectal polyps
  - Hemorrhoids
- Skin.
  - Eczema
    - Possible association with food allergy
  - Lesions, such as purpura and petechiae
    - Bleeding disorders
    - HSP
    - HUS

DIFFERENTIAL DIAGNOSIS

Newborns

- Usually appears as rectal bleeding or blood suctioned from the stomach during routine postnatal care.
- In many instances, no lesion is readily discernible, and bleeding resolves spontaneously and permanently.
- Common causes of GI bleeding in the first 24 hours of life include
  - Maternal blood swallowed during delivery
  - Local trauma after nasogastric suctioning
- Preterm newborns who have low Apgar scores are at increased risk for gastric ulcerations and erosions that can bleed.
  - These lesions rarely are primary.
  - Usually result from asphyxia associated with a difficult delivery, a cardiac lesion, or sepsis.
- Hemorrhagic disease of the newborn.
  - Inherited deficits of coagulation factors or delay in administration of postnatal vitamin K occasionally produces GI bleeding.
  - More commonly, these disorders show as diffuse bleeding from venipuncture sites.
- NEC usually manifests as lower GI bleeding with bilious vomiting, abdominal distention, and lethargy.
  - Symptoms usually occur after the first feeding but may be delayed for a few weeks.
  - Most common in preterm newborns.
  - Occasionally occurs in stressed full-term newborns.
  - Up to 5% of neonates in intensive care units develop NEC.
  - Overall mortality may be as high as 30%.
  - Complications include sepsis and shock.
- Intrinsic structural lesions can cause lower GI bleeding.
  - Duplication
    - A tubular structure lined with normal GI mucosa adjacent to the true intestine can be present anywhere along the GI tract.
    - Can cause lower GI bleeding, acute or chronic, along with abdominal distention and vomiting.
    - Unrepaired duplications may lead to obstruction, volvulus, or perforation.
  - Volvulus or malrotation
    - A volvulus or malrotation of the GI tract should be suspected in any neonate who has abdominal pain, bilious vomiting, and melena.
    - Because these symptoms and signs are often unreliable, the diagnosis should be considered in any newborn who vomits and has guaiac-positive stools.
  - Vascular malformation
    - Must be considered in the evaluation for painless rectal bleeding.
      - Hemangiomas
      - Other vascular lesions, such as hereditary hemorrhagic telangiectasia (Rendu-Osler-Weber syndrome)

- The most common form is the larger cavernous hemangioma.
  - Polypoid or diffuse
  - Extends several centimeters through the submucosa of the small or large intestine
- The diffuse type usually involves the large bowel, specifically the rectum.
- Cutaneous vascular malformations are often present but may require scrupulous searching to detect.
- Can occur anywhere along the GI tract.
- Produce slow or diffuse lower GI bleeding.
- The bleeding is usually painless.
- The color of the blood in the stool varies, depending on the level of the lesion.
- Vascular malformations may be associated with cutaneous hemangiomas or cardiac defects.

- Milk protein allergy or soy protein allergy.
  - Can begin as early as the first week of life
  - Exhibits as
    - Severe diarrhea
    - Gross blood in the stool
    - Abdominal distention
    - Vomiting
  - Older neonates may have occult lower GI bleeding and mucus in the stool.
  - The diagnosis is made by clinical response to withdrawal and rechallenge with the offending protein.
- Infectious enteritis.
  - Rare in the newborn.
  - May appear later in the first month of life.
  - In very young neonates, bacterial gastroenteritis, especially that caused by *Salmonella* species, can cause bloody diarrhea with or without fever.
  - 8%–13% of neonates may have associated bacteremia.
- Anal fissure.
  - Suggested by bright-red blood streaks on the surface of the stool.
  - Often associated with hard stools.
  - The most common cause of rectal bleeding.
  - Visual inspection of the anus usually confirms the diagnosis.

Infants and Young Children

Upper GI Bleeding

- Upper GI bleeding in the young child usually is caused by mucosal lesions in the esophagus and the stomach.
- Esophageal bleeding.
  - Often slow and occult (without hematemesis), manifesting with signs of anemia or guaiac-positive stools
    - Acid reflux.
      - Newborns who have persistent or severe gastroesophageal reflux can develop esophagitis.
    - Viral or fungal infection, particularly with immunocompromised patients.
    - Caustic ingestion severe enough to burn the esophageal mucosa can result in painful swallowing, drooling, oral burns, and hematemesis.
      - Esophageal foreign body.
        - As infants become more mobile and dexterous, they are at higher risk for foreign body and toxic ingestions.
        - Coins and small toys, when lodged in the esophagus, can cause drooling, vomiting, and chest pain.
        - Persistent or unrecognized esophageal foreign bodies
          - Lead to edema and erosion of the esophagus.
          - May cause hematemesis.
    - Mallory-Weiss tear.
      - A rent at the gastroesophageal junction that may result from forceful or prolonged vomiting.
      - The emesis becomes streaked with bright-red blood and may develop into coffee-ground emesis if the tear persists.
- Gastroesophageal varices.
  - Variceal bleeding ranges from slow, persistent oozing to acute massive hematemesis.
    - If the cause of the portal hypertension is extrahepatic, the bleeding may be well tolerated.
    - In patients with cirrhotic liver disease, bleeding may lead to rapid hepatic decompensation.
    - Chronic liver diseases may also be associated with coagulopathy and thrombocytopenia from the hypersplenism that often accompanies them.
  - Physical examination usually reveals signs of portal hypertension, such as enlarged liver or spleen, or both.

- Most cases result from the cavernous transformation of the extrahepatic portion of the portal vein, which has been associated with
  - Umbilical vessel catheterization
  - Omphalitis
  - Neonatal conditions associated with hypoxia, prolonged jaundice, or sepsis
- Intrahepatic causes of cirrhosis, leading to portal hypertension, that may first show during childhood include
  - Wilson disease (>6 years)
  - α_1-Antitrypsin deficiency
  - Biliary cirrhosis
  - Metabolic, infectious, or anatomic forms of chronic liver disease

- Gastritis.
  - Infectious
  - Medications (eg, nonsteroidal anti-inflammatory drugs [NSAIDs], corticosteroids)

Lower GI Bleeding

- The differential diagnosis is broad.
- Polyps.
  - Juvenile polyps
    - Most common cause of lower GI bleeding in 3- to 7-year-olds.
    - Typically located in the colon.
    - Simple, solitary, benign hamartomatous lesions.
    - May irritate the GI tract, causing intermittent, painless, bright-red rectal bleeding.
    - Many of these polyps auto-amputate if left alone and are passed with the stool.
    - Most polyps are located within 25 cm of the anus.
    - They often can be identified by
      - Digital examination
      - Air-contrast barium enema
      - Sigmoidoscopy
    - Can be removed with snare electrocautery.
  - Adenomatous polyps
    - Adenomatous polyps are premalignant tumors.
    - May transform into cancer over an average of 10 years.
    - May produce rectal bleeding as early as infancy.
    - Managed differently from juvenile polyps.
    - Associated with familial polyposis and Gardner syndrome.
    - Juvenile polyposis coli (JPC) is suggested by the presence of 5–10 juvenile polyps; ≥10 polyps is considered diagnostic.
      - JPC occurs in about 10% of patients with colonic polyps.
      - Associated with anemia, right-colon polyps, and adenomas.
- Meckel diverticulum.
  - A remnant of the omphalomesenteric duct.
  - Found within 2 feet of the ileocecal valve.
  - Present in up to 2% of the population.
  - Acid secreted by ectopic gastric mucosa, which is usually present in diverticula that bleed, causes peptic ulceration of the ileal mucosa.
    - Typically occurs in children <3 years.
    - Causes painless, maroon- or red-colored lower GI bleeding.
    - Typically, bleeding is severe enough to cause the hemoglobin level to decrease to ~8 g/dL.
- Intussusception.
  - Telescoping of an intestinal segment.
  - Typically seen in children 6–24 months of age.
  - Often idiopathic.
  - Usually involves invagination of the distal ileum through the ileocecal valve into the colon.
  - Older children with intussusception and those with multiple recurrences may have pathologic lesions that serve as lead points (eg, Meckel diverticulum, polyp, tumor).
  - Classic presentation begins with intermittent, severe, crampy abdominal pain, with vomiting shortly thereafter.
  - As the intussusception progresses, lethargy or paradoxical irritability develops.
  - Guaiac-positive stools.
    - Seen as the bowel becomes ischemic
    - May progress to the passage of red bloody mucus, classically referred to as *currant jelly stools*
  - Complications include
    - Intestinal perforation
    - Peritonitis
    - Significant bleeding
- Lymphonodular hyperplasia.
  - May cause painless, blood-streaked stools.
  - Usually seen in children <6 years.
  - May be associated with food allergy.
  - Diagnosis is made by endoscopic examination and histologic confirmation.

- Infectious enterocolitis.
  - Symptoms range from mild diarrhea to fever, abdominal cramping, and watery or mucoid stools (or both forms) with or without blood.
  - *Salmonella, Shigella, Yersinia,* and *Campylobacter* species are the most common bacterial causes of bloody diarrhea.
  - Pseudomembranous colitis, caused by *Clostridium difficile,* also causes fever, diarrhea, abdominal cramping, and bloody stools.
    - The child often has a history of recent hospitalization and antimicrobial therapy.
    - Onset of symptoms can be delayed for weeks.
  - A variety of parasites, such as *Entamoeba histolytica* and *Trichuris trichiura*, can cause bloody diarrhea.
- Systemic diseases.
  - HSP: purpura with arthritis, hematuria, abdominal cramping, and bloody stool
  - HUS: prodrome of hemorrhagic colitis, followed by thrombocytopenia, hemolytic anemia, and renal disease
    - Most commonly caused by Shiga toxin-producing *Escherichia coli* O157:H7
- Other causes.
  - Milk protein allergy, anal fissures, and congenital GI structural anomalies can also occur in this age group.

Older Children and Adolescents

Upper GI Bleeding

- Nasopharyngeal bleeding
- Esophagitis
- Mallory-Weiss tear
- Gastroesophageal varices
- Gastritis
  - Infectious
  - Medications (eg, NSAIDs, corticosteroids, tetracycline)
- Peptic ulcer disease
  - Can occur at any age but more common in the older child and adolescent.
  - Symptoms usually begin with epigastric or periumbilical pain accompanied by nausea.
  - GI bleeding is evident in ~50% of children as hematemesis or melena.
  - *Helicobacter pylori* bacteria found in the gastric mucous layer or adherent to the epithelial lining of the stomach are causally associated with ulcers.

Lower GI Bleeding

- Polyps
  - Juvenile (see Lower GI Bleeding under Infants and Young Children)
  - Adenomatous (see Lower GI Bleeding under Infants and Young Children)
- Infectious enterocolitis (see Lower GI Bleeding under Infants and Young Children)
- IBD
  - May appear in the adolescent age group as episodes of bloody diarrhea, cramping, and tenesmus.
  - The course may be atypical in children, making the diagnosis difficult.
  - Abdominal pain, fever, and weight loss suggest IBD.
  - The diagnosis is also suggested by
    - Growth failure
    - Anemia
    - Evidence of recurrent bouts of GI bleeding
- Systemic diseases (HSP, HUS)
- Vascular malformation
- Meckel diverticulum (see Lower GI Bleeding under Infants and Young Children)
- Hemorrhoids
- Anal fissure

False Bleeding

- Red color in the stool often is assumed to be blood; however, many other substances cause change in stool color.
  - Foods that contain a high concentration of red pigments, such as tomatoes, cranberries, beets, and red fruit juices and gelatin (eg, Jell-O).
  - Red-colored medications, such as acetaminophen and amoxicillin, can be passed in the stools, especially if diarrhea is present.
  - Spinach, licorice, iron, and bismuth (eg, Pepto-Bismol) often lead to dark, black stools, which can be confused with true melena.
- In infants, *Serratia marcescens* can cause red diaper syndrome as a result of the formation of red pigment in soiled diapers stored for >1 day.

Non-GI Sources of Bleeding

Neonates

- A neonate may swallow maternal blood during delivery or when breastfeeding if the mother has bleeding nipples.
  - The Apt test is helpful in differentiating maternal blood from neonatal blood.
    - One part of the bloody stool (or gastric aspirate) is mixed with 5 parts of water to lyse the erythrocytes.
    - After the mixture is centrifuged, 1 mL of 0.2 normal sodium hydroxide is added to the supernatant hemoglobin solution.
    - After 2 minutes, fetal hemoglobin, which resists the alkaline reduction, remains pink, whereas maternal hemoglobin turns yellow-brown.
    - Melena contains denatured hemoglobin and, therefore, cannot be used for the Apt test.
- Vaginal bleeding in a newborn with estrogen withdrawal may be mistaken for rectal bleeding.

Older Children

- Swallowed blood usually is the result of nosebleeds or bleeding mouth lesions.
  - This nasopharyngeal bleeding can mimic hematemesis or melena.
- Pulmonary hemorrhage.
  - Rare in children
  - May exhibit acutely as hematemesis
  - May exhibit more chronically as melena and anemia
- In the menstruating teenager, vaginal blood may affect the accuracy of stool guaiac testing.
- The possibility of blood being added to the stool by a caregiver suggests Munchausen syndrome by proxy.

LABORATORY EVALUATION

- Laboratory testing should focus on
  - Determining the amount and duration of the bleeding
  - Assessing for coagulopathy
  - Evaluating for other laboratory abnormalities that may be associated with the underlying disease process
- Initial laboratory studies.
  - Complete blood cell count with reticulocyte count
    - Hemoglobin determination can help assess the degree of blood loss.
    - Acute bleeding may not decrease the hemoglobin level until intravascular equilibration has taken place.
    - The leukocyte count may be elevated in infectious colitis.
  - Coagulation studies
    - Prothrombin time may be elevated as a sign of a bleeding disorder or as result of abnormalities in liver synthetic function.
    - Partial prothrombin time.
    - Platelet count.
  - Serum chemistries
    - To assess renal function.
    - An elevated blood urea nitrogen level may result from increased intestinal absorption of blood with long-standing upper GI bleeding.
  - Liver function tests for suspected liver disease
  - Blood type and screen
    - If patient has significant bleeding or a low hemoglobin level, transfusion may be needed.
  - Stool specimen
    - If bloody diarrhea is present
    - For culture, if appropriate
    - For ova and parasites, if appropriate
  - Stool guaiac
    - The most common test.
    - Highly sensitive.
    - Uses the peroxidase activity of hemoglobin to catalyze a color change on a test card or paper strip.
    - Can identify even trace amounts of blood.
    - Foods that have peroxidase activity may cause false-positive results if eaten within 3 days of testing.
      - Red meat
      - Liver
      - Processed meats
      - Raw fruits and vegetables, especially melon, turnip, radishes, and horseradish
    - High vitamin C intake interferes with the peroxidase reaction and can cause false-negative results.
    - Outdated guaiac cards and prolonged storage may affect the accuracy of the test.
    - Heme testing of emesis should be done with guaiac cards with a buffered stabilized hydrogen peroxide solution (eg, Gastroccult).
      - Stool guaiac cards are not accurate because gastric acid can affect the reaction that causes the color change.

- Serologic tests
  - *H pylori* immunoglobulin G antibodies are often unreliable.
    - Should be reserved for use when duodenal or gastric ulcers have been definitively diagnosed by endoscopy or radiography
  - IBD serologies.

IMAGING

- Imaging studies are needed in most children with GI bleeding
  - To locate the source of the bleeding
  - To confirm a suspected diagnosis
- The type of study is chosen on the basis of
  - Child's age
  - Clinical presentation
  - Possible diagnosis
- Radiography
  - Plain radiographic films
    - Usually are nonspecific
    - Usually require additional imaging to confirm a diagnosis
  - 2-view (flat and upright) abdominal radiographs will reveal
    - Signs of obstruction or calcifications
    - Air-fluid levels
    - Dilated bowel loops
  - Some specific radiographic findings include
    - Pneumatosis intestinalis in NEC.
    - Intestinal obstruction with absence of gas in the right colon in intussusception.
    - In volvulus/malrotation, radiograph may show loops of small bowel overriding the liver shadow, with paucity of air in the GI tract distal to the volvulus.
- Barium studies
  - For identification of
    - Intestinal foreign bodies
    - Polyps
    - Lymphonodular hyperplasia
    - IBD
  - An upper GI series, barium enema, or both are sometimes needed to confirm the diagnosis of volvulus/malrotation.
  - Barium swallow has poor sensitivity in esophagitis.
  - Barium enema or upper GI series with small-bowel follow-through should be the last studies performed.
    - They make use of arteriography, isotope scans, and endoscopy impossible for several days thereafter.
  - Confirmation of intussusception, followed by hydrostatic reduction with barium or air enema, is successful in about 70%–80% of cases, even in those with symptoms for >24 hours.
- Ultrasonography
  - Screening ultrasonography has decreased unnecessary enemas for clinically suspected intussusception.
    - Diagnosis can be confirmed by identification of the layering of intestinal mucosa as a bull's-eye or coiled spring lesion.
- Color Doppler ultrasonography
  - Increasingly useful as a diagnostic aid in intussusception and malrotation.
  - Usefulness depends on the skill of the operator.
- Computed tomography (CT)
  - Occasionally helpful in defining related anatomic features if the child is hemodynamically stable and cooperative or sedated.
  - Midgut volvulus also may be diagnosed by CT or ultrasonography.
    - Duodenal dilation
    - Fixed midline bowel
    - Wrapping of the bowel and the superior mesenteric vein around the superior mesenteric artery (whirlpool sign)
- Angiography
  - For severe, life-threatening bleeding.
  - Can be diagnostic and therapeutic, depending on the ability to embolize the bleeding vessels.
  - Limited sensitivity in detecting slow or past bleeding, so best performed when bleeding is active.
  - Selective arteriography or digital subtraction angiography may aid in demonstrating vascular malformation.
- Arteriography
  - If the bleeding is not immediately life threatening
  - Can demonstrate bleeding that occurs at a rate ≥0.5 mL/min
- Radionuclide scanning
  - For children with persistent, active bleeding who are clinically stable.
  - Often can identify the source of an acute, ongoing bleed by pinpointing accumulation of an isotope at the bleeding site.
  - Sulfur-colloid isotopic study.
    - More sensitive and less invasive than arteriography.
    - Can demonstrate active bleeding at rates as low as 0.05–0.10 mL/min.

- Demonstrates active bleeding by using a tracer with a very short half-life.
- Isotope is extracted rapidly so that background radioactivity is low.
- In small neonates and infants, a large uptake of the isotope by the liver may mask the right upper quadrant.

- The bleeding site may be determined with technetium Tc 99m pertechnetate–labeled red blood cells.
  - Labeled cells may remain in circulation for more than a day and allow repeated imaging to locate the site of intermittent bleeding.
  - An isotope-labeled red blood cell infusion has a lower contrast ratio but is better at detecting slower or intermittent bleeds than a sulfur-colloid isotopic scan.
  - A Meckel scan uses technetium Tc 99m pertechnetate, which is secreted by ectopic gastric mucosa, to identify the diverticulum.
    - The test is fairly sensitive but only during active bleeding.
    - A repeat scan is sometimes necessary.
- If the rate of bleeding does not permit enough time to perform these studies, vasopressin or octreotide may be administered parenterally in an attempt to control the bleeding and to stabilize the patient.

- Wireless capsule endoscopy is used for evaluation of the small intestine, primarily in obscure GI bleeding in children as young as 2 years.
  - In one study, >50% of children had the source of obscure bleeding identified, including
    - Ulcerative jejunitis
    - Polyps
    - Angiodysplasia
    - Blue rubber bleb nevus syndrome
    - Meckel diverticulum
  - Limitations include the size of the standard capsule to be swallowed and risk for retention in strictured areas of the small bowel.

DIAGNOSTIC PROCEDURES

- Upper GI fiber-optic endoscopy can establish diagnosis in 75%–90% of patients.
  - Adequate visualization is unlikely if bleeding is massive and cannot be controlled with saline lavage.
  - Gastric ulceration is diagnosed in newborns by radiography or upper GI endoscopy.
- Gastroduodenoscopy to determine source and type of lesion present if bleeding ceases.
- Sigmoidoscopy with persistent rectal bleeding to identify polyps or mucosal lesions.
  - Bleeding from above the reach of the sigmoidoscope indicates the need for other diagnostic studies.
- Colonoscopy and biopsy usually confirm diagnosis of IBD.
- Esophagoscopy and pH probe manometry are used to diagnose gastroesophageal reflux.
- *H pylori* infection is diagnosed by culture of biopsy specimens from the stomach and duodenum.

TREATMENT APPROACH

- The approach to acute massive GI bleeding must be the same as that in any other emergency.
  - Obtain pertinent historical information.
  - Perform a brief but adequate examination.
  - Stabilize the patient clinically.
  - Arrive at a working diagnosis.
  - Institute appropriate therapy or consultations.
- Massive upper GI bleeding may lead to vomiting, aspiration, and airway obstruction requiring stabilization of the airway with endotracheal intubation.
- Administration of oxygen is always indicated.
- Assess adequacy of circulation by evaluating
  - Peripheral perfusion
  - Quality of pulses
  - Capillary refill time
- In children, the initial response to hypovolemic shock is tachycardia.
- In acute bleeding, adequate blood pressure can be maintained with blood loss of up to 30% without replacement.
- Prompt surgical intervention is required
  - In vascular compromise of the intestine
  - When the rate of bleeding is excessive and uncontrollable by more conservative methods
- Conservative measures control most acute episodes of GI bleeding relatively easily.
  - Patients who eventually require surgical intervention can usually undergo surgery electively at a later time.

SPECIFIC TREATMENT

Emergency Management

Immediate Response

- Tachycardia and capillary refill time are essential in determining the nature of the resuscitation required.
- Skin turgor and the color of the mucous membranes should be noted.

- Place at least 1 (preferably 2) large-bore intravenous (IV) catheters if there are signs of shock.
  - Orthostasis or frank hypotension
  - Tachycardia
  - Poorly perfused extremities
  - Pale mucous membranes
- If percutaneous venous access is not obtained within a few minutes, an intraosseous line should be placed.
  - 20 mL/kg of physiologic (normal) saline solution should be given rapidly to re-expand the vascular volume.
  - Fluid bolus may need to be repeated several times.
  - Additional fluid should be given as needed.
  - With >30%–40% acute blood loss, packed red blood cells should be given as soon as possible.
- A nasogastric tube, preferably of the vented sump type, helps to
  - Determine the source of bleeding.
  - Estimate the volume of ongoing blood loss.
- The nasogastric tube should be left in place and attached to
  - Low-pressure continuous suction, if vented
  - Intermittent suction, if non-vented
- Nasogastric tube placement may aggravate bleeding in a patient with varices.
  - Even in this case, a nasogastric tube may be required to quantitate blood loss adequately.

Controlling Bleeding and Determining Specific Diagnosis

- If the nasogastric aspirate contains blood or if the patient has hematemesis
  - Saline irrigation may be instituted through the nasogastric tube to decrease mucosal blood flow and stop profuse bleeding.
  - The efficacy of lavage in decreasing and controlling gastric bleeding has not been demonstrated conclusively.
    - It allows easier assessment of the rate of bleeding.
    - It helps in removing clotted blood.
    - Prolonged lavage (>10 minutes) may not allow fibrin clots to form at bleeding site.
  - Use saline at room temperature, because irrigation with water can lead to hyponatremia and iced or cold fluid may cause hypothermia.
  - Withdraw after 3–5 minutes.
  - Aspirate returns that do not clear in 10 minutes
    - Suggest continued GI bleeding.
    - Should prompt additional evaluation.
- Gastroduodenoscopy if bleeding ceases
  - To demonstrate the bleeding source.
  - To determine the type of lesion present.
  - Upper GI fiber-optic endoscopy can establish the diagnosis in 75%–90% of patients.
  - Adequate visualization is unlikely if the bleeding is massive and cannot be controlled with saline lavage.
- If the bleeding is not immediately life-threatening
  - Arteriography can demonstrate bleeding that occurs at a rate ≥1 mL/min.
  - Sulfur-colloid isotopic study, more sensitive and less invasive than arteriography, can demonstrate active bleeding at rates as low as 0.05–0.10 mL/min.
  - Injection with technetium Tc 99m pertechnetate–labeled red blood cells that may remain in the circulation for more than a day and allow repeated imaging can be used to locate the site of intermittent bleeding.

Mucosal Erosion or Inflammation

- Antacid therapy, with or without concomitant use of a histamine$_2$ (H_2)-blocker
- For bleeding ulcers, IV therapy with a proton-pump inhibitor
  - Reduces risk of rebleeding
  - Does not appear to influence overall mortality rate

Variceal Bleeding

- The cause of the lesions must be determined for appropriate treatment of the underlying disease.
- In particular, liver or portal venous disease should be sought.
- Clotting factors and platelets should be replaced as indicated.
- Use of balloon tamponade with a Sengstaken-Blakemore tube is effective in controlling bleeding but has a high incidence of complications.
- Vasoactive drugs and endoscopy have replaced the Sengstaken-Blakemore tube in most cases.
  - Somatostatin and octreotide (a synthetic peptide with similar properties).
    - Octreotide decreases splanchnic blood flow, thereby decreasing portal pressure.
    - Pediatric studies (with no control groups) have shown octreotide to be 50%–63% effective in controlling acute variceal bleeding.

- Initially, a 1 mcg/kg (maximum of 50 mcg) bolus is infused, preferably through a central or intraosseous line, followed by an infusion of 1 mcg/kg/h, which may be increased by 1 mcg/kg/h up to 4 mcg/kg/h.

- Endoscopy is the preferred intervention for variceal bleeding because it can provide diagnosis and therapy.
  - Endoscopic injection sclerotherapy (EIS) uses an injection of a sclerosing solution into the varices.
  - Endoscopic variceal band ligation (EVL) uses elastic bands placed around the varices in the distal esophagus.
  - Endoscopy has been found to be 80%–100% effective in controlling variceal bleeding.
    - In a randomized controlled trial in 49 children, EVL achieved variceal eradication faster than EIS, with a lower rebleeding rate and fewer complications.
  - Endoclips are a newer technique used in severe GI bleeding, applied to the mucosa through a flexible endoscope to compress tissue around a bleeding vessel.
  - Endoscopy should be performed by an experienced gastroenterologist, with general anesthesia and endotracheal intubation available, especially when performed in small children.

- Studies in adults and experience in pediatrics, although limited to date, suggest
  - Octreotide as the initial treatment for bleeding varices.
  - Followed by endoscopic therapy: EVL or EIS.
  - If bleeding continues despite vasoactive and endoscopic therapies, balloon tamponade can be attempted.

H pylori Infection

- Treatment, when indicated, consists of
  - A 7- to 14-day course of any of a variety of antibiotic regimens
  - A proton-pump inhibitor

NEC

- Neonates remain hospitalized for bowel rest and IV antibiotics.
- Occasionally requires surgical intervention.

Meckel Diverticulum

- Treatment requires surgical excision.

Mallory-Weiss Tear

- Although bleeding is minor and usually resolves spontaneously, an H_2-blocker may be needed to prevent continued irritation by stomach acid.

Volvulus Malrotation

- Immediate surgical repair is necessary.

WHEN TO REFER

- Upper GI bleeding
- Lower GI bleeding
  - Of moderate amount
  - Persistent or intermittent

WHEN TO ADMIT

- Any nontrivial upper GI bleeding
  - Active bleeding
  - Moderate amount of blood
  - Anemia
  - Abdominal pain
- Significant lower GI bleeding
- Hemodynamic instability
- Anemia (hematocrit)
- Severe abdominal pain
- Associated systemic symptoms (eg, HUS, IBD)
- Altered mental status or lethargy
- Suggestion of surgical etiology (eg, Meckel diverticulum, intussusception, volvulus)

Gluten-Sensitive Enteropathy (Celiac Disease)

DEFINITION

- Celiac disease (CD), also known as celiac sprue or gluten-sensitive enteropathy (GSE), is characterized by clinical features of malabsorption and pathologic changes in the jejunal mucosa.
  - Both improve when gluten is removed from the diet and recur when it is reintroduced.
- Second most common cause of malabsorption in children after cystic fibrosis.

DIFFERENTIAL DIAGNOSIS

- Common causes of flat villus lesions include
  - Food sensitivity
  - Cow's milk protein allergy
  - Soy protein allergy
  - Eosinophilic gastroenteritis
  - Infection: viruses (*Rotavirus*), bacteria (*Escherichia coli*), parasites (*Giardia lamblia*), or fungi (*Candida albicans*)
  - Malnutrition (kwashiorkor, not marasmus)
  - Tropical sprue
  - Immunodeficiency disorders (most notably AIDS)
  - Familial enteropathy
  - Lymphoma
  - Crohn disease
  - Whipple disease
- A sweat test should be performed to exclude cystic fibrosis.
  - Most common cause of malabsorption in childhood
  - May coexist with GSE

DIAGNOSTIC APPROACH

- For a definitive diagnosis of CD, the following criteria must be met:
  - Demonstration of clinical malabsorption and abnormal intestinal lesions
  - Clinical and histologic response to gluten withdrawal
  - Subsequent gluten challenge that may exacerbate clinical symptoms but that always produces abnormal intestinal histologic findings
- Diagnosis must be made with certainty because
  - CD means lifelong gluten restriction.
  - Untreated patients have a higher risk of gastrointestinal cancer in late adulthood.

LABORATORY FINDINGS

- Serologic markers for diagnosis and screening.
  - Symptomatic patients, with biopsy.
  - Screening of asymptomatic patients at risk.
    - First- and second-degree relatives
    - Those with other disorders associated with high prevalence of CD
  - Supportive evidence for the disease.
  - Monitor dietary compliance.
- Antiserum tissue transglutaminase (tTG) antibodies.
  - First step in screening
  - 95% specificity in children >2 years; 88% specificity in children <2 years
- Immunoglobulin A (IgA) endomysial antibodies (EMA)
  - Most specific.
  - Used as a confirmatory test when findings of tTG antibody testing are equivocal.
  - When IgA is low or absent, consider measuring serum tTG-IgG and EMA antibody-IgG levels.
- Antigliadin antibodies.
  - Less specific and less sensitive than EMA
  - Can be helpful to use with tTG antibody panel in children <2 years
- False-positive EMA and tTG antibody tests are unusual.
  - False-positive EMA result with normal tissue biopsy could indicate poor tissue sampling, distal small bowel disease, or latent disease.
  - Although tTG has high specificity, rarely, other immune disorders will also have positive tTG antibodies: type 1 diabetes mellitus, Crohn disease, ulcerative colitis, autoimmune hepatitis, severe heart failure, arthritis, collagen vascular disorders.
- Genetic testing.
  - *HLA-DQ2* and *HLA-DQ8*.
    - 30% of the population has a positive *HLA-DQ2* and might never develop CD.
  - Negative test result excludes CD.
    - Positive test results in patients who are asymptomatic and have normal biopsy results present a diagnostic and management dilemma.
  - Testing is recommended for
    - Patients on a gluten-free diet (GFD) for >3 months prior to any testing and refusing a gluten challenge
    - Patients with equivocal changes on the intestinal biopsy

  - High-risk groups with other autoimmune disorders who want to avoid long-term serologic screening (type 1 diabetes mellitus is an exception, as these patients can share the same genetic background)
  - Screening of family members who do not want periodic serologic screening
- Hematology and electrolytes.
  - Anemia.
  - Hypoprothrombinemia.
  - Abnormal serum albumin and globulin levels.
  - Electrolyte disturbances, especially hypokalemia.
  - Calcium, phosphorus, and alkaline phosphatase levels may be outside reference range in patients with rickets.

IMAGING

- Radiographic findings in CD are nonspecific.
  - May see distended small intestine and segmented barium on a small-bowel follow-through

DIAGNOSTIC PROCEDURES

- 4 endoscopic markers have been described in CD pathogenesis that help to make the diagnosis and have sensitivity from 47%–100%, depending on the severity of disease.
  - Scalloping
  - Micronodularity
  - Loss of folds
  - Mosaic pattern
- Biopsy of the small intestine is the best way to diagnose CD.
  - Should be performed to confirm diagnosis when serologic markers are positive.
  - Routinely obtained by fiberoptic endoscopy, permitting visualization of the duodenum.
    - In young infants, edema of the duodenal mucosa is more common.
  - Biopsies from the second portion of the duodenum have the highest yield.
    - A recent recommendation to increase test sensitivity is to obtain duodenal bulb biopsies as well, as CD has a patchy and proximal-to-distal distribution.
- Repeat biopsy and rechallenge.
  - Not necessary if a child >2 years has become asymptomatic on GFD and is undergoing serum monitoring.
  - Children with an indeterminate diagnosis should undergo another biopsy to demonstrate healing followed by rechallenge and another biopsy.
- Video capsule endoscopy.
  - Used to visualize the whole small bowel, as CD rarely can present with distal distribution, making the classic diagnostic approach difficult.
  - Should be considered in children with
    - Normal histology and positive serology results
    - Indeterminate diagnosis
    - Symptoms despite a GFD, especially alarm symptoms, such as fever, weight loss, and pain

TREATMENT APPROACH

- Treatment of GSE is a GFD.
  - Remove gluten from the diet, including wheat, rye, and barley.
    - Oats do not contain gluten but may be cross-contaminated with gluten during manufacturing.
  - A lactose-free diet is advocated during the initial 4–6 weeks to alleviate diarrhea.
    - Lactose may be gradually reintroduced, provided there is no concurrent infection, severe electrolyte imbalance, dehydration, or celiac crisis.
  - Nutrition counseling by a qualified dietitian is an important component of treatment.
- Replacement iron, folic acid, vitamin K, vitamin D, and calcium should be initiated when appropriate.
- Compliance with GFD can be tracked by assessing serologic markers.
  - The initial identified positive antibody should be tested every 6 months until the patient has had 2 consecutive negative tests, and annually thereafter.
  - An increase in tTG antibody will be observed if the patient is noncompliant.
  - Weeks may be required for symptoms to disappear completely; subjective improvement occurs within the first few days.

WHEN TO ADMIT

- Failure to thrive and intractable diarrhea
- Dehydration and electrolyte abnormalities
- Celiac crisis

WHEN TO REFER

- Referral to a gastroenterologist is based on
  - Clinical suspicion
  - Presence of positive serologic markers
  - First-degree relatives with GSE
  - Syndromic presentations
  - Existence of other autoimmune disorders

FOLLOW-UP

- After GFD, monitoring serum tTG or EMAs (or both) is the preferred method for children >2 years.

COMPLICATIONS

- Celiac crisis
  - Triggers include
    - Severe malnutrition
    - An infectious process
    - Poor compliance with a GFD
    - Bacterial overgrowth caused by dysmotility
    - Hypoproteinemia
  - Patient needs to be admitted to the intensive care unit for further stabilization of electrolytes and fluids.
  - Once fluids have stabilized, start parenteral nutrition with total gut rest.
  - Slowly, introduction of a GFD with oral supplementation of iron, folic acid, vitamin D, and calcium should be attempted.
  - These patients might require prolonged total parenteral nutrition.

PROGNOSIS

- GSE means lifelong gluten restriction.
- Untreated patients risk developing gastrointestinal cancer in late adulthood.
- Refractory GSE occurs in 7%–30% of patients.
  - Patients resistant to a GFD require therapy with immunomodulators.

DEFINITION

- Headaches fall into 4 patterns.
  - Acute and recurrent
  - Simple acute
  - Chronic progressive
  - Chronic nonprogressive

HISTORY

- Assess disability of child using, as measures, absenteeism and presenteeism.
  - *Absenteeism* refers to the number of days missed from school, work, or after-school activities.
  - *Presenteeism* refers to days when, although present, the child cannot learn or fully participate.
- Detailed headache history.
  - Length of time the child has had headaches
  - Severity
  - Quality
  - Location
  - Frequency
  - The effect on the child's quality of life and disability
  - Factors that exacerbate and relieve the headaches
  - Any aura before headaches
- Detailed review of systems.
- Past medical history.
- A psychosocial and family history to identify contributory stressors.

PHYSICAL EXAMINATION

- Look for systemic symptoms.
  - Arrest of growth, puberty, or menstruation
  - Lesions of the skin suggestive of neurocutaneous disorder
- On neurologic examination, look for
  - Abnormalities of optic discs
  - Impaired extraocular movements
  - Ataxia on gait
  - Impaired rapid nose-to-finger movement
  - Asymmetric reflexes

DIFFERENTIAL DIAGNOSIS

- Acute and recurrent
  - Most common.
  - Characterized by periods of normalcy between attacks.
  - Severe attacks accompanied by autonomic symptoms (nausea/vomiting, photophobia or phonophobia) ensure the diagnosis of migraine.
  - Milder attacks are called *tension-type headaches* (TTHs).
- Simple acute
  - Less of a diagnostic dilemma, with cause usually apparent
    - For example, meningitis, encephalitis, systemic viral or bacterial infection
- Chronic progressive
  - Symptoms that get worse and worse over weeks should alert the physician that a tumor or other serious pathology looms.
  - Pain is often worse in the morning and gets a little better as the day goes on.
  - Systemic or neurologic signs and symptoms further add to the worry.
- Chronic nonprogressive
  - Evolves from a previous headache pattern or presents without previous headache history.
  - In *transformed* or *chronic migraine,* there is a history of prior acute intermittent headache accompanied by autonomic symptoms.
  - In *chronic TTH* (CTTH), there is a history of episodic TTH.
  - With no history of migraine attacks, triptans have no role in this condition.
  - In *new daily persistent headaches* (NDPHs), the daily headache comes out of nowhere, often after a viral syndrome or mild head trauma.
  - Patients with the chronic nonprogressive pattern of headache require imaging because there is no return to normalcy between attacks.

IMAGING

- Magnetic resonance imaging (MRI) is not required for children and adolescents with a history of migraine who have a normal neurologic examination.
- MRI is needed for patients with systemic symptoms, abnormal neurologic features on history or examination, abrupt onset of severe headache, or changes in pattern to a more chronic headache.

TREATMENT APPROACH

Migraine Principles for Management

- Patients with migraine have a more sensitive brain and are more sensitive to internal and external triggers.
  - In many instances, unhealthy lifestyle habits serve as a trigger for childhood headaches.
    - Inadequate nutrition
    - Skipping meals
    - Altered sleep patterns

- Maintaining healthy lifestyle habits include
  - Adequate fluid hydration, with limited use of caffeine.
  - Regular exercise.
  - Adequate nutrition through regular meals and a balanced diet.
  - Adequate sleep.
  - The patient and parents must understand that these objectives are lifetime goals that can control the effect of migraines and minimize the use of medication.
  - Lifestyle changes may result in an overall long-term improvement in quality of life and may reverse any progressive nature of the disease.

- Treat attacks at first twinge.
  - Medications work best the earlier they are given.
  - School nurse needs to know that when a child asks for medication it should be given immediately, not after a trial wait to see if the child feels better.
- Treat attacks with high doses of oral medication.
  - A migraine starts a few hours before the patient notices; in particular, the stomach has delayed emptying.
  - Sufficient medication should be given to ensure that an adequate dose passes through the gastroparetic stomach.
- Do not wait until you are sure it is a migraine.
  - Children with migraines who have a TTH still respond to triptans.
- Involve teachers and nurse.
  - Children are in school for a large portion of their lives.
- Triptans are OK.
  - Only a few triptans (sumatriptan nasal spray and eletriptan tabs) have US Food and Drug Administration approval for use by children.
  - But triptans are safe, demonstrating excellent efficacy without negative outcomes.
- Who needs prophylaxis?
  - A follow-up visit should be scheduled within 2–6 weeks to determine if progress has been made with initial therapy.
  - If absenteeism and presenteeism have not diminished to an acceptable level, the child should receive a long-term treatment plan, either non-pharmacologic or pharmacologic.
- When to refer.
  - A primary care physician should be able to prescribe medication and recommend lifestyle changes and a prevention modality.
  - If no improvement, referral is indicated.

Chronic Daily Headache Principles for Management

- Rule out intracranial pathology.
  - Unlike migraine, chronic daily headache requires neuroimaging with MRI.
- Identify pattern: transformed migraine versus CTTH versus NDPH.
  - With transformed migraine, migraine spikes still occur and will respond to triptans.
  - CTTHs do not respond to triptans.
  - Patients with NDPHs may or may not have migraine spikes. If so, use triptans; if not, do not.
- Remove acute medications overused on a daily basis.
  - Overuse of analgesics can itself lead to headaches.
  - Stopping an overused medication can be done cold turkey or gradually over the course of a month or so.
  - If removed acutely, the medication should be replaced by comfort measures (eg, intranasal dihydroergotamine [DHE], a long-acting triptan) because headaches will get worse for a few days.
  - With gradual tapering, the patient and family should be warned that there may be spikes of worsening headache during the process.
- Start or reinforce healthy headache habits.
- Child should stay in school.
- Start a non-pharmacologic or pharmacologic intervention.
- Watch for undetected depression or anxiety.
- When to refer.
  - Ideally, all children and adolescents with chronic daily headache should be seen by a specialist.
    - When one is not available, the principles herein can guide initiation of treatment with timely follow-up.
    - If there is no improvement, referral is necessary.
  - Primary physicians should be familiar with community mental health resources, acupuncturists, physical therapists, and therapists with expertise in biofeedback and relaxation training.

SPECIFIC TREATMENT

Short-term Therapy

- Short-term therapy is designed to ameliorate the episodic headache.
- The goal of this treatment is a quick return to normal activity without relapse.
- For headache in children, medications include
  - Nonsteroidal anti-inflammatory drugs (NSAIDs)
    - Ibuprofen, naproxen sodium
      - Ibuprofen has become a mainstay for the acute treatment of childhood headaches and migraines.
      - Good tolerability.
      - Effective in clinical trials.
      - Proper use of ibuprofen requires
        - Identification by the child of headache onset
        - Initiation of rapid treatment
        - Proper dosing based on weight
        - Avoidance of overuse; limited to ≤3 times per week
    - Aspirin for older children
    - General pain relievers, eg, acetaminophen
- Most prescriptive nonspecific medications have not been evaluated in children or have not been proven effective.
- Many prescriptive medications contain sedatives or narcotics that may treat the pain but do not allow the child to return to normal functioning.
- When NSAIDs are ineffective or not completely effective, migraine-specific therapy is often required.
- Triptans.
  - Triptans are 5-$HT_{1B\text{-}1D}$ agonist migraine-specific medications.
  - Currently, 7 triptans have been approved for use in the United States in adults.
    - Not approved for use in childhood migraine.
    - Several studies in children, however, have shown their effectiveness.
  - Sumatriptan, zolmitriptan, rizatriptan.
    - Two treatment methods may be used when prescribing triptans: rescue therapy or stepwise treatment within an attack.
    - The child starts with an NSAID at an appropriate dose at the onset of the headache.
      - If this medication is not working, a triptan is used as rescue therapy.
    - The stratified care model requires the patient to determine the headache severity at the onset.
      - For a mild or moderate headache, the patient takes an NSAID.
      - For a severe headache, the patient takes a prescribed triptan.
      - In this way, patients stratify their headaches and the subsequent treatment.
      - This method has not been successful in young children because they often have difficulty recognizing the headache severity at its onset.
- DHE.
  - Ergot alkaloids have a long history of usefulness in migraines.
  - Frequently used in the emergency management of childhood headaches.
  - Limited reports have shown usefulness of intravenous DHE in an inpatient setting.
    - Breaks status migrainosus or prolonged migraines in children.
    - The effect may be enhanced if patients are premedicated with dopamine antagonists.
- Dopamine antagonists (prochlorperazine, metoclopramide).
  - Initially used for nausea and vomiting effects of migraine headaches.
  - The dopaminergic model of migraine was developed, and these medications have been reanalyzed for usefulness in short-term therapy of the headaches themselves.
  - Dopamine antagonists should be given intravenously.
  - Their utility is limited by extrapyramidal side effects.
  - It is suggested that prochlorperazine can be used to break an acute episode of status migrainosus.
    - Best given with rehydrating fluids in the emergency department (ED) setting

Prophylactic Treatment

- The second component of effective headache treatment.
- Should be instituted when the headache or migraine becomes frequent or disabling.
- Goals.
  - Minimize the effect of the headache.
  - Reduce the number of headaches.
- A clear diminishment in severity and headache features may be observed.

- Having >2–3 headaches per month typically warrants treatment.
- For all prophylactic medications, titrate doses slowly to an effective level.
  - Requires understanding by the patient and family that this may be a lengthy process (weeks, months)
  - Failure to respond may be due to
    - Inadequate time of treatment
    - Inadequate dosing
- Prophylactic medications can be grouped into
  - Antiepileptics
    - Only divalproex sodium and topiramate are currently approved for the prevention of migraines in adults; they are not approved for children.
    - Divalproex sodium.
      - 15–20 mg/kg/d
    - Topiramate.
      - 2–4 mg/kg/d.
      - Taper up to this dose slowly, in quarter steps, over 8–10 weeks.
    - Gabapentin.
    - Levetiracetam.
    - Zonisamide.
  - Antidepressants
    - The most widely used tricyclic antidepressant for headache prevention is amitriptyline.
    - Has been used for many decades for its antidepressive properties.
    - First recognized in the 1970s as an effective migraine therapy.
    - Most studies in children with amitriptyline have been open-label studies; there are no placebo-controlled studies.
      - Amitriptyline was found to be effective in 50%–60% of children in a crossover study comparing amitriptyline with propranolol and cyproheptadine.
      - In an open-label study, amitriptyline resulted in a perceived improvement in >80% of the children.
    - Titrate slowly to the full dose over 8–10 weeks to minimize side effects, particularly somnolence.
    - Nortriptyline has been used instead of amitriptyline.
      - Potential for increased arrhythmias.
      - Regular electrocardiographic evaluation may be required if nortriptyline is chosen.
    - Selective serotonin reuptake inhibitors have been studied for the treatment of headaches in adults; they have not yet been studied in children.
      - Effectiveness is not as notable as that of tricyclic antidepressants.
      - Suggests that a more global decrease in neurotransmitter reuptake inhibition is needed to treat childhood headache disorders.
  - Anti-serotonergic medications
    - Cyproheptadine has long been used for preventing childhood headaches.
      - Antihistamine with anti-serotonergic effects.
      - May have some calcium channel–blocking properties.
      - Tends to be well tolerated.
      - Increased weight gain is the most significant side effect.
        - Because weight gain is substantial, use of this medication tends to be limited to younger children.
  - Antihypertensive medications
    - β-Blockers have a long history of use for preventing childhood headaches.
      - Propranolol was found to provide mixed responsiveness when used for childhood headaches.
    - Even with their long history, β-blockers have limited usefulness in children.
      - They cause a decrease in blood pressure.
      - There is a risk for exercise-induced asthma.
      - They can result in depressive effects.
    - Calcium channel blockers have been extensively studied in adults for headache prevention.
      - Flunarizine has been demonstrated to be an effective migraine preventive agent.
        - Available in Europe but not in the United States.
        - Baseline headache frequency was significantly reduced in flunarizine-treated children.
        - These data cannot be extrapolated to other calcium channel blockers.

Biobehavioral Therapy

- Third component of effective headache treatment.
- Essential for children to maintain a lifetime response to the treatment and management of their headaches.
- Biobehavioral therapy can be divided into 3 components.

- Treatment adherence.
  - A clear understanding by the patient and parent about the importance of the treatment is essential.
- Psychological or biobehavioral intervention may be useful in assisting with adherence by identifying roadblocks to the medical plan and helping to overcome these barriers.
- Biofeedback-assisted relaxation therapy.
  - May be a useful addition.
  - For children, single-session biofeedback-assisted relaxation therapy has been demonstrated to be learned quickly and efficiently.

WHEN TO REFER

- Headaches that do not respond routinely to acute treatment
- Headaches that are increasing in frequency, severity, or duration
- Headaches in which the features acutely change
- Side effects of medications that limit increasing the medication to an effective dose
- Psychological factors that interfere with management
- Disability that impairs functioning

WHEN TO ADMIT

- Admission or ED treatment should be considered when
  - Home therapies are ineffective for acute treatment.
  - Headache has continued for >24 hours.
  - Headache pain becomes intolerable.

FOLLOW-UP

- Important to regularly assess the morbidity of headaches and effectiveness of treatment.
- Regular measurement of disability and quality of life are helpful in assessing treatment strategies and improvement in outcomes.
  - Disability
    - Pediatric Migraine Disability Assessment uses a patient-based disability scale.
  - Quality of life
    - Pediatric Quality of Life Inventory version 4.0 uses parent and child input.
      - Evaluates functioning in health, emotional, social, and school domains.
      - Headaches have been found to substantially affect emotional development and school functioning.

COMPLICATIONS

- Avoiding overuse of medication is critical in short-term therapy.
- Overuse can cause analgesic rebound headaches.
  - Transformed migraines
  - Chronic daily headaches
- Overuse of medication is characterized by inadequate treatment of headache.
  - Low-dose or delayed treatment.
    - Increase in analgesic use over time, with decreased effectiveness
  - When rebound headaches are identified, a recovery period free of analgesic use is required.
- Allodynia.
  - A painful or heightened sensation beyond the location of the headache.
  - Once allodynia has been established, patients have decreased response to medication.
  - For these patients, stress the need for early treatment.

PROGNOSIS

- Short-term studies show great improvement for episodic and chronic headache with appropriate treatment.
- There are no long-term studies tracking childhood migraine or chronic daily headache cohorts.

DEFINITION

- Pediatricians must recognize the signs, symptoms, and risk factors for hearing loss and become aware of appropriate referral paths.
  - Pediatricians are usually the first health care practitioners approached by parents who have concerns about their child's hearing.
  - Parents become concerned about their infant's hearing at ~6 months of age when the hearing loss is severe.
  - Milder degrees of hearing loss typically do not generate concern until the child reaches school age.
  - Patterns of hearing loss that are termed *mild* or *minimal* are far from benign and cause academic, communicative, social, and emotional difficulty for school-aged children.

HISTORY

- ~35%–50% of children with hearing loss have no known risk factors.
- Although most congenital hearing loss is hereditary, a negative family history is common.
- Complete history and observation accompanied by hearing screening are essential.
- Significant speech and language delays, because of their association with severe to profound hearing loss, provide a high level of suspicion.
- A history of any of the following conditions should also prompt screening for hearing loss:
  - Behavioral problems
  - Social difficulties
  - Academic difficulties
- Parents' comments and potential explanations for mild to moderate hearing loss include
  - "He can hear me when he wants to hear me. Sometimes he just ignores me."
    - — With mild hearing loss, little or no difficulty listening in quiet settings
    - — More difficulty when background noise is present
  - "When I call her, she has to look around for me. She never seems to know where I am in the house."
    - — With unilateral hearing loss, difficulty localizing a sound source
  - "When we are in crowds, I have to call his name several times before he responds."
    - — Difficulty hearing in the presence of background noise
  - "My child is exhausted when she comes home from school."
    - — Fatigue from the effort exerted to listen throughout the day
  - "His speech is very difficult to understand. I don't think it's his hearing because he always responds when I call him."
    - — Children with high-frequency hearing loss may have poor speech production.
      - ■ They cannot hear high-frequency speech sounds (consonants).
      - ■ They can hear low- and mid-frequency sounds.
  - "My child is doing poorly in school, but I know she understands the material because we go over her homework at night."
    - — Difficulty hearing in school settings because of background noise
    - — No hearing difficulty apparent when working at home in a one-on-one situation

DIFFERENTIAL DIAGNOSIS

- Most congenital hearing loss is hereditary.
  - Evidence of the gene expression can be highly variable.
  - Most children with inherited hearing loss are nonsyndromic.
  - Children with dominantly inherited hearing loss may have families who demonstrate incomplete penetrance.
- 20% of children with congenital hearing loss have associated syndromes (eg, Alport, Waardenburg) or progressive loss (eg, Usher syndrome).
- Children with Down syndrome are at high risk for conductive hearing loss and have a higher-than-average risk for sensory loss.
- Infants in the neonatal intensive care unit are at increased risk for
  - Neural conduction dysfunction
  - Auditory brain stem dysfunction
  - Auditory neuropathy/dyssynchrony
    - — A recently identified disorder characterized by a unique constellation of behavioral and physiologic auditory test results.
    - — Normal outer cochlear hair cell function, but dyssynchronous signal firing at the level of eighth cranial nerve.
    - — Ranges from normal hearing to profound hearing loss and poor speech perception.

  - Aside from infants who receive intensive neonatal care, those with family history of childhood hearing loss or with hyperbilirubinemia are at particular risk.
  - Most affected infants do not benefit from hearing aids but do benefit from cochlear implantation.
- A child with unilateral hearing loss may reach age-appropriate speech and language milestones but experience difficulty in the presence of background noise on school entry.
- A child with high-frequency hearing loss would be expected to develop speech and language in a timely manner but with distortions or omissions of high-frequency consonant sounds.
  - Parents may report the child has difficulty in the presence of background noise but seems to have little difficulty in quiet settings.

DIAGNOSTIC PROCEDURES

- If an infant or child fails a hearing, speech, or language screening measure in the pediatrician's office, referral for a full audiologic evaluation is recommended.
- The Joint Committee on Infant Hearing (JCIH) recommends following a 1-3-6 rule for identification and intervention for congenital hearing loss.
  - All newborns should have access to hearing screening by 1 month of age.
  - Confirmation of hearing loss by 3 months of age.
  - Early intervention services by 6 months of age.
- A recent study suggested that more than half of children who failed screenings in primary care practices did not receive rescreening or referral for further testing.
- Audiologists with pediatric experience can define degree of hearing loss.
  - Distinguish among conductive, sensory, and neural types of loss in children of all chronologic ages and developmental levels.
- Evaluation of hearing in infants and young children consists of a combination of physiological and behavioral measures.
  - For infants <6 months, testing is typically limited to physiologic measures because behavioral responses are not yet reliable enough to define the extent of loss.

TREATMENT APPROACH

- Early identification of hearing loss is of little value without timely intervention.
- Many children have conductive and sensorineural hearing losses not amenable to medical treatment; they may benefit from amplification.

SPECIFIC TREATMENT

Hearing Aids

- Traditional hearing aids are designed to
  - Pick up sounds.
  - Convert them to electrical signals.
  - Amplify, filter, and convert signals back to acoustic signals for a receiver.
  - In noisy settings, frequency-modulated systems can be used alone or in combination with hearing aids.
    - For instance, a microphone worn by a teacher to amplify only the teacher's voice while minimizing interfering background noise.

Cochlear Implants

- An alternative to traditional hearing aids.
- The device is surgically implanted in the cochlea.
  - Electrodes stimulate the auditory nerve with electrical current.
- Cochlear implants do not restore normal hearing.
- Children are eligible for implants at age 1 year, although some exceptions can be made.
- Children vary markedly in the benefits they derive from the implant.
  - Those who receive implants at an early age tend to benefit more than those who receive implants at older ages.
  - All are considered at risk for pneumococcal meningitis.
  - Most experience at least an awareness of sound.
  - Some reach a high level of speech recognition and can develop normal speech and language skills.

WHEN TO REFER

- The 2007 position statement of the JCIH lists risk indicators for delayed-onset hearing loss. Children whose medical history includes ≥1 of the following indicators should be referred for audiologic testing:
  - Caregiver concerns about hearing, speech, language, or developmental delay.
  - Family history of permanent childhood hearing loss.

- Neonatal intensive care >5 days or any of the following conditions regardless of length of stay:
  - Extracorporeal membrane oxygenation
  - Assisted ventilation
  - Exposure to ototoxic medications (gentamycin and tobramycin) or loop diuretics (furosemide)
  - Hyperbilirubinemia that requires exchange transfusion
- In utero infections, such as cytomegalovirus, herpes, rubella, syphilis, and toxoplasmosis.
- Craniofacial anomalies, including those that involve the pinna, ear canal, ear tags, ear pits, and temporal bone anomalies.
- Physical findings (eg, white forelock) that are associated with a syndrome known to include a sensorineural or permanent conductive hearing loss.
- Syndromes associated with hearing loss or progressive or late-onset hearing loss, such as neurofibromatosis, osteopetrosis, and Usher syndrome; other frequently identified syndromes include Waardenburg, Alport, Pendred, and Jervell and Lange-Nielson.
- Neurodegenerative disorders, such as Hunter syndrome, or sensory motor neuropathies, such as Friedreich ataxia and Charcot-Marie-Tooth disease.
- Culture-positive postnatal infections associated with sensorineural hearing loss, including confirmed bacterial and viral meningitis.
- Head trauma, especially basal skull/temporal bone fractures that require hospitalization.
- Chemotherapy.

FOLLOW-UP

- For infants with permanent hearing loss.
  - Communicate with the state's coordinator for early hearing detection and intervention to ensure that the infant and family are enrolled in appropriate services.
  - Be sure the infant has received a thorough medical evaluation (including genetics consultation) to determine the cause of the hearing loss.
- There is a high incidence of vision problems in children with hearing loss.
  - Referral for ophthalmologic evaluation may be warranted.
- ~30%–40% of children with hearing loss have additional disabilities.
  - Periodic developmental screening and surveillance is an integral part of their management.

COMPLICATIONS

- Children with hearing loss are especially vulnerable to the effects of otitis media with effusion because additional hearing loss can negatively affect the audibility of speech through hearing aids.
- Closely monitor and manage children who have persistent otitis media with effusion.

Heart Murmurs

DEFINITION

- A heart murmur is a sound heard between heart sounds and is produced by turbulent blood flow.

HISTORY

- A complete and accurate history is the most important aspect of evaluating a cardiac murmur in children because the clinical context in which the murmur occurs provides clues to the cause of the heart murmur.
- History should include the patient's chief complaints and
  - Medical history
  - Birth history
  - Family history
- Patient history.
  - Poor weight gain
  - Difficulty feeding
  - Frequent respiratory difficulties
  - Respiratory distress
  - Cyanosis
  - Exercise intolerance
  - Chest pain with exercise
  - Unexplained syncope (especially syncope resulting in injury)
  - Concurrent syndromic disorder or genetic disease
  - Concurrent metabolic disorder or storage disease
  - Sickle cell anemia or blood dyscrasias resulting in anemia
  - History of cardiotoxic chemotherapy
  - Concurrent HIV disease
  - Hypertension
- Birth history.
  - Maternal diabetes
  - Maternal TORCH (**t**oxoplasmosis, **o**ther agents, **r**ubella, **c**ytomegalovirus, **h**erpes simplex) infections during pregnancy
  - Multiple-gestation pregnancy
  - In vitro fertilization pregnancy
  - Maternal drug use (legal or illicit), known teratogens
  - Abnormal amniocentesis
  - Abnormal fetal ultrasonogram
  - Maternal history of congenital heart disease
- Family history.
  - Congenital heart disease
  - Sudden cardiac death
  - Unexplained death in young people
  - Hypertrophic cardiomyopathy
  - Infantile Marfan syndrome

PHYSICAL EXAMINATION

Patient Evaluation

- Evaluation of a cardiac murmur involves more than auscultation of the heart.
- Complete physical examination is needed to put the murmur in perspective.
- Pertinent aspects of physical examination include
  - Vital signs
    - Temperature, heart rate, respiratory rate, length/height, weight
    - Blood pressures in the right arm, left arm, leg
    - Pulse oximetry on room air (right hand and either foot, if infant)
  - General
    - Cyanosis, pallor, dysmorphic features, overall distress
    - Breathing pattern: retractions, grunting, nasal flaring
  - Head and neck
    - Jugular venous distention
    - Thyromegaly, thyroid nodules
  - Chest
    - Chest wall deformity, asymmetry, surgical scars
    - Lung aeration
    - Rales, rhonchi, wheezes, stridor
  - Cardiac
    - Inspection
    - Palpation
    - Auscultation
  - Abdomen
    - Liver span
    - Tenderness
    - Distention, ascites
  - Extremities
    - Perfusion: capillary refill, temperature, quality of pulses
    - Clubbing, cyanosis, edema
    - Arachnodactyly, joint laxity (Marfan syndrome)
    - Increased arm span/upper to lower body ratio (Marfan syndrome)

Cardiac Evaluation

- Includes
  - Inspection
  - Palpation
  - Auscultation

- Inspection
  - Begin with
    - General appearance
    - Nutritional status
    - Genetic abnormalities
    - Color
    - Comfort
  - Then inspect the chest wall for abnormalities, including
    - Deformities, such as pectus excavatum
    - Asymmetry
    - Surgical scars
  - Palpation
    - Begin with the extremities to assess
      - Perfusion
      - Pulses
      - Capillary refill
      - Temperature of extremities
  - The precordium is then palpated to detect the point of maximal impulse (PMI) and to detect thrills.
    - Under normal conditions, the PMI represents the activity of the left ventricle and is palpated in the left fourth or fifth intercostal space in the midclavicular line.
    - Activity of the right ventricle is appreciated in the fourth to fifth intercostal space along the left lower sternal border.
    - Abnormal intensity or location of the PMI or of the right ventricle's activity is suggestive of a cardiac anomaly.
    - Thrills can be palpated
      - In the suprasternal notch (suggesting aortic valve disease or coarctation of the aorta)
      - Along left upper sternal border (suggesting pulmonary valve disease)
      - Along right upper sternal border (suggesting aortic valve disease)
      - Along left lower sternal border, in association with ventricular septal defects (VSDs)
- Auscultation
  - A systematic approach to auscultation of the heart ensures that each major anatomic area of the heart is heard in systole and diastole.
  - The major areas of auscultation on the precordium.
    - Apex
    - Left lower sternal border
    - Left mid or upper sternal border
    - Right upper sternal border
  - These areas correspond to each atrioventricular and semilunar valve, as well as the outflow tracts of the right and left ventricles.
  - The clinician should also auscultate
    - Left and right infraclavicular areas
    - Axillae
    - Back
  - Auscultation for systolic or continuous blood flow noises (bruits) should be performed over the liver and fontanel.
    - A bruit suggests an arteriovenous malformation.
  - The patient should be examined in the following positions:
    - Supine
    - Sitting
    - Left lateral decubitus
  - Other postural maneuvers that may be useful include
    - Squatting
    - Standing
    - While performing a Valsalva maneuver
  - Auscultation includes an assessment of S_1 and S_2, including the nature of the splitting of S_2.
  - Consideration of any S_3 and S_4, murmurs, clicks, and rubs completes the auscultation.

Evaluation of Heart Murmur

- A heart murmur is usually the result of turbulent blood flow.
- Random fluctuations in velocity and pressure during blood flow results in vibration of the surrounding tissue, which is auscultated as a murmur.
- A complete description of a heart murmur includes
  - Intensity
  - Timing
  - Location
  - Radiation
  - Quality

Intensity

- Graded on a scale of 1–6 for murmurs in systole.
  - Grade 1: barely audible
  - Grade 2: soft but easily audible
  - Grade 3: moderately loud without a thrill
  - Grade 4: moderately loud with a thrill
  - Grade 5: loud with a thrill, heard with stethoscope partly on the chest
  - Grade 6: loud with a thrill, heard with stethoscope off the chest

- Some cardiologists use a scale of 1–4 for murmurs in diastole.
  - Grade 1: barely audible
  - Grade 2: soft but immediately heard
  - Grade 3: easily heard
  - Grade 4: very loud
- The intensity of a murmur does not necessarily reflect the severity of abnormality.
- A small VSD may have a very loud murmur.
- Critical aortic stenosis may have a very soft murmur if cardiac output is low.

Timing

- The point in the cardiac cycle at which the murmur is heard.
- Murmurs are described as being
  - Systolic
  - Diastolic
  - Continuous
- Systolic murmurs occur between atrioventricular valve closure (S_1) and semilunar valve closure (S_2).
- Systolic murmurs are further divided into
  - Ejection (crescendo-decrescendo) murmurs
    - Begin shortly after S_1, peak in intensity.
    - End at or before S_2.
    - May be innocent or abnormal.
    - All innocent systolic ejection murmurs are grade 1–3.
    - Abnormal murmurs result from
      - Obstructed blood flow across a semilunar valve (aortic or pulmonary stenosis), in which case an ejection click may usher in the murmur.
      - Excessive volume crossing a normal semilunar valve without associated clicks.
    - Abnormal murmurs may be of any grade of intensity.
  - Holosystolic (pansystolic, S_1 coincident) murmurs
    - Start with S_1.
    - Continue to S_2 at the same level of intensity.
    - Sometimes obscure S_2.
    - Result from movement of blood from a higher-pressure chamber to a lower-pressure chamber, such as with a VSD or mitral regurgitation.
  - Late systolic murmurs
    - Associated with mitral valve prolapse and resultant mitral regurgitation
    - Classically preceded by a mid- or late-systolic click
- Diastolic murmurs occur between semilunar valve closure (S_2) and atrioventricular valve closure (S_1).
  - Diastolic murmurs are divided into early, mid, and late diastolic murmurs.
  - All are pathologic and require referral to a pediatric cardiologist.
  - Early diastolic murmurs begin immediately after S_2 and are decrescendo in nature, becoming less audible as the ventricle fills.
  - Aortic insufficiency and pulmonary insufficiency are heard in early diastole.
  - Mid-diastolic murmurs occur during the rapid ventricle filling.
  - Mitral stenosis and tricuspid stenosis murmurs are heard in mid-diastole.
  - Late diastolic (presystolic) murmurs occur near the end of diastole, during atrial contraction.
  - Severe mitral stenosis or tricuspid stenosis murmurs increase in late diastole.
- Continuous murmurs.
  - Extend across portions of systole and diastole.
  - Vascular in origin.
  - Caused by
    - Aortopulmonary connection (eg, patent ductus arteriosus)
    - Arteriovenous connection (eg, arteriovenous malformation)
    - Turbulent flow in collateral arteries (eg, coarctation of the aorta)
    - Turbulent flow in veins (eg, venous hum)
    - Surgical shunt
  - These murmurs are pathologic, except for the innocent venous hum (**Table 1**).
  - Tend to wax and wane in intensity through the cardiac cycle, often diminishing in late diastole.
- A to-and-fro murmur describes an ejection murmur heard in systole, coupled to a decrescendo murmur early in diastole.
  - To-and-fro murmurs are not true continuous murmurs.
  - Combined aortic stenosis and aortic insufficiency or combined pulmonary stenosis and pulmonary insufficiency produce to-and-fro murmurs.

Location and Radiation

- Refers to the area where the murmur is best heard and where it radiates.
- *Radiation* means the murmur is also audible with unexpected intensity at some distance from its location.
- Useful in differential diagnosis.

Table 1. Common Innocent Murmurs

Murmur	Intensity	Timing	Location	Quality
Still	1–3/6	Early–mid systolic	LM-LLSB or apex	Vibratory, musical
Pulmonary	1–3/6	Early–mid systolic	LUSB	Low-pitched, ejection flow
Venous hum	1–3/6	Continuous	Right or left infraclavicular or supraclavicular	Low-pitched, disappears with head turn, supine position, jugular compression

Abbreviations: LM-LLSB, left mid to left lower sternal border; LUSB, left upper sternal border.

Quality

- Refers to the pitch and nature of a murmur.
- Pitch is generally described as high or low.
  - High-pitched murmurs occur when the pressure differential involved is large.
    - Aortic insufficiency is a high-pitched murmur.
  - Low-pitched murmurs occur when a lower pressure differential is involved.
    - Pulmonary insufficiency is a low-pitched murmur.
- Systolic murmurs are described as harsh, blowing, musical, or vibratory.
- Diastolic murmurs are described as blowing, rumbling, crescendo, or decrescendo.

DIFFERENTIAL DIAGNOSIS

- The challenge for the primary care physician lies in distinguishing innocent murmurs from those that indicate a cardiac abnormality.
- Location helps narrow the differential diagnosis of the murmur.
- Radiation of the murmur can also aid in forming the differential diagnosis.
  - Murmurs that radiate to the neck tend to be of aortic or left ventricular outflow tract origin.
  - A murmur heard best at the left upper sternal border with radiation to the axillae and back is more likely to be pulmonary in origin.
- Postural maneuvers are useful in distinguishing among different types of murmurs.
  - Innocent murmurs tend to become louder when the patient moves from an upright to a supine position.
  - Placing the patient in the left lateral decubitus position increases the murmur of mitral stenosis.
  - Valsalva maneuver, by decreasing venous return
    - Makes the murmur of aortic stenosis softer
    - Makes the murmur of hypertrophic obstructive cardiomyopathy louder
    - Decreases the murmurs associated with a VSD and mitral regurgitation
    - Can nearly eliminate innocent Still murmurs (See **Table 1.**)
  - Squatting increases venous return and makes the murmur of hypertrophic obstructive cardiomyopathy softer.
  - Standing up after squatting can accentuate the murmur or click of mitral valve prolapse by moving the murmur and click closer to the S_1.
  - Recumbent positioning or turning the head can eliminate the innocent continuous murmur of a venous hum.

LABORATORY EVALUATION

- Patients with cyanotic heart diseases are polycythemic, with very high hemoglobin level and hematocrit.

IMAGING

- Chest radiograph may be done to determine the size of heart, status of pulmonary vasculature, and evidence of congestive cardiac failure.

DIAGNOSTIC PROCEDURES

- Electrocardiography and echocardiography are usually done to define the cause of a pathologic murmur.

TREATMENT APPROACH

- It is important to differentiate innocent murmur from abnormal murmur.
  - Once innocent murmur is established, reassurance is the mainstay of management.

SPECIFIC TREATMENT

- The specific management of cardiac murmur depends on the underlying cardiac lesion.

WHEN TO REFER

- Patient, maternal, or family history that raises the index of suspicion for heart disease.
- All diastolic murmurs require referral to a pediatric cardiologist.
- Continuous murmurs, except venous hum.
- All systolic murmurs grade 4 or higher.
- All systolic murmurs not clearly fitting the pattern of innocent murmur.
- Auscultation of an S_4 gallop.
- A thrill is an abnormal finding and warrants referral to a pediatric cardiologist.
- Cyanosis, clubbing.
- Higher blood pressure in one or both arms than a leg.
- Congestive heart failure—rales, respiratory distress, hepatomegaly, edema.
- Abnormal electrocardiogram.
- Symptoms that suggest reactive airway disease that do not improve with appropriate medical therapy.

DEFINITION

- Infantile hemangioma is a benign tumor that begins developing after birth.
  - Although not a malignancy, infantile hemangioma may require treatment and follow-up to prevent functional and aesthetic sequelae.

HISTORY

- Diagnosis of hemangioma is primarily clinical and based on history.
- Demographic, prenatal, and perinatal factors in patients with these lesions may provide clues to pathogenesis.
  - Classical presentation is shortly after birth, with or without an initial precursor lesion or "herald patch."
    - Bruise-like patch
    - Limited area of pallor with fine telangiectasia
    - Macular erythematous lesion
    - May be erroneously attributed to trauma
  - Several phases of unpredictable duration follow, characterized by a proliferative phase, a plateau phase, and, finally, some degree of an involution phase.
    - A rapidly growing vascular tumor, within the first 1–2 months of life, characterizes the proliferative phase.
    - While most growth is completed by 3–6 months, growth can continue to 9 months of life.
    - In the plateau/early involution phase, clinical changes include color fading, softening, and reduction in volume.
    - Involution continues with a decreased volume of tumor; however, this process may take several years and is often incomplete.
    - Many infantile hemangiomas leave behind residual cutaneous telangiectasia, scarring, fibrofatty residuum, or excess skin.

PHYSICAL EXAMINATION

- Clinical appearance depends on which level of the skin is affected.
  - Superficial cutaneous
  - Deep
  - Segmental plaque-like
- Superficial cutaneous hemangiomas.
  - Previously named "strawberries."
  - Classical raised, red lesions with a thin epidermal surface layer, which is fragile and prone to injury.
  - During the rapidly proliferative phase, ulceration is possible because the thin epidermal layer can easily become traumatized.
- Deep lesions.
  - Located in the deeper dermis and subcuticular space.
  - Perceived color is generally darker.
  - Visible telangiectasia, dilated small vessels, or vascular papules can be associated, especially with draining veins at the periphery.
- Flat, plaque-like segmental lesion (less common).
  - Grows radially but does not develop into the more classical "fleshy" appearance
  - Warrants further evaluation in certain anatomic locations

High-risk Lesions

- Segmental hemangioma
  - Large segmental hemangiomas in the facial region warrant consideration for PHACES syndrome.
    - **P**osterior fossa malformations
    - **H**emangiomas of the face
    - **A**rterial anomalies
    - **C**ardiovascular anomalies
    - **E**ye anomalies
    - **S**ternal clefting
  - Lumbar or pelvic segmental hemangioma may be associated with LUMBAR syndrome.
    - **L**ower body hemangioma
    - **U**rogenital anomalies
    - **U**lceration
    - **M**yelopathy
    - **B**ony deformities
    - **A**norectal malformations
    - **A**rterial anomalies
    - **R**enal anomalies
- Visceral hemangioma
  - The presence of >5 lesions can be associated with visceral involvement.
  - Intra-abdominal hemangioma.
    - Most often manifests as a liver hemangioma, which is the most common pediatric hepatic lesion.
    - The presenting feature clinically could be high-output cardiac failure.
  - Rapidly involuting congenital hemangioma (RICH).
    - Single, large lesion detected by antenatal imaging, physical examination, or imaging at birth.

  - May be asymptomatic or associated with high-flow shunts causing high-output cardiac failure.
- Multifocal lesions.
  - May be asymptomatic or may demonstrate high flow, causing high-output cardiac status.
  - Should be treated with propranolol and followed closely.
  - Many multifocal or closely packed, diffuse hemangiomas may cause consumptive hypothyroidism, which should always be investigated and treated aggressively if found.

■ Upper airway hemangioma
- Sometimes called subglottic hemangioma.
- Significant risk of airway compromise during the proliferative phase.
- Patients usually present clinically with stridor.
- About half of these neonates will have a cutaneous lesion, but those with perioral lesions seem to be at highest risk.
  - 60% of those with a "beard distribution" lesion will develop symptomatic upper airway difficulty.
  - Respiratory failure can occur precipitously and warrants prompt referral to a pediatric otolaryngologist.

■ Periocular hemangioma
- ≤50% of periocular hemangiomas are amblyogenic.
  - Most commonly from refractive error (astigmatism, anisometropia) resulting from pressure on or tumor infiltration of optic structures
- Infrequently, the lesion covers the visual field.
- These lesions must be urgently evaluated by an ophthalmologist to prevent irreversible amblyopia.

■ Massive hemangioma
- Hypothyroidism has been described secondary to high levels of type 3 iodothyronine deiodinase within the lesion.
- In patients with large or multiple lesions, investigation of thyroid function may be required.

DIFFERENTIAL DIAGNOSIS

■ Other types of vascular tumors
- RICH
  - Presents fully grown at birth.
  - Detectable on prenatal ultrasound.
  - Commonly a single, raised tumor that has a dark color, central telangiectasia, and radial distribution of ectatic veins and is surrounded by a pale halo region.
  - Lesions do not grow, and they involute by 12–18 months.
- Non-involuting congenital hemangioma
  - Presents fully grown at birth.
  - Detectable on prenatal ultrasound.
  - Solitary tumor usually found on the head and neck or lower limbs.
  - Resembles RICH clinically; grows with the patient or expands slightly over time but does not regress.
- Pyogenic granuloma
  - Although presenting at any age, these were often known as "pregnancy tumors" and may be related to trauma.
  - More commonly found in children, these grow rapidly to vascular and friable papules or tumors.
  - Usually on the head and neck, but other sites have been described.
  - Lesions often ulcerate, bleed, and are prone to recurrence with subtotal treatment.
- Tufted angioma
  - Uncommon vascular tumors usually present in infancy or childhood but have been found congenitally
  - Diffuse group of lesions including solitary tumors, large plaques or port-wine stain–like lesions with a cobblestone presentation
  - Associated with Kasabach-Merritt syndrome (systemic coagulopathy resulting from thrombocytopenia)
- Kaposiform hemangioendothelioma
  - Rare entity; may be found in skin or as a retroperitoneal tumor.
  - Presents as a congenital tumor or develops shortly after birth.
  - Histologic examination demonstrates dense and infiltrating spindle cell nodules with infrequent mitoses.
  - Associated with Kasabach-Merritt syndrome.

■ Vascular malformations (especially in deep lesions)
- When a lesion is present at birth, vascular malformation should be considered.
  - Congenital structural anomalies that represent abnormal vasculature or lymphatics.
  - Lesions grow in proportion to the child.

- May only present with clinical symptoms or signs or proliferate during periods of hormonal fluctuation (adolescence, pregnancy).
  - — Capillary malformation
  - — Venous malformation
  - — Lymphatic malformation
  - — Arteriovenous malformation
  - — Mixed malformations
- Other tumor types, if presenting with a subcutaneous mass
  - Lipoma
  - Neurofibroma
  - Rhabdomyosarcoma

IMAGING

- Doppler ultrasonography.
  - May demonstrate a well-circumscribed mass, within which are anechoic channels and numerous fast-flow vessels.
  - Flow should be correlated with the clinical stage of the lesion.
    - — Arterial flow will be reduced during the involutional phase.
    - — Throughout the proliferative phase, there are numerous vessels with a high Doppler shift (>2 kHz), low resistance, and nonspecific echogenicity.
  - Recommended in children with >5 lesions to identify visceral involvement.
- Magnetic resonance imaging (MRI).
  - Lesions causing a diagnostic dilemma.
  - Presurgical planning to determine anatomic relationships between the tumor and the surrounding tissues.
  - Characteristic findings.
    - — Well-circumscribed, uniformly enhancing, and densely lobulated structures with multiple flow voids
    - — Dilated arterial feeding and venous draining vessels at the periphery or within the center of the lesion
  - In children with multiple lesions, MRI should be performed only if ultrasonography shows lesions that suggest another diagnosis.
- Plain radiography rarely aids in diagnosis.

DIAGNOSTIC PROCEDURES

- Biopsy
  - Rarely, to exclude other pathology

TREATMENT APPROACH

- Hemangiomas can be classified as high risk (functional or aesthetic complications) or low risk (no functional or aesthetic concern).
  - High-risk lesions should be treated aggressively to prevent long-term complications (functional and aesthetic).
  - Complete involution is often unlikely.
  - Early treatment may prevent possibly severe adverse sequelae.

SPECIFIC TREATMENT

Observational Management

- Low-risk lesions.
- Regular visits to the primary care physician during the proliferative period.
  - Monitoring.
  - Reassurance.
  - Photographic aids describing hemangioma natural history should be used to limit parental anxiety.
- A multidisciplinary approach may be helpful, involving dermatologists, plastic surgeons, general surgeons, ophthalmologists, otolaryngologists, and other health care professionals.

Medical Management

- Corticosteroids
  - Mainstay of treatment for the past 40 years.
  - Administered systemically or intralesionally.
  - Treatment is most effective in the rapidly proliferative phase.
  - Despite the complication profile, dramatic results have been found with corticosteroid administration, purportedly as a result of angiogenesis inhibition.
- β-Blockers
  - Propranolol is a nonselective β-blocker.
  - Numerous case series have found promising results in all 3 phases: proliferative, plateau, and involutional.
  - Mechanism is uncertain.
  - Has been administered orally at 2 (range 1–3) mg/kg/d in twice-daily or 3-times daily dosing.
  - Topical delivery has been tried with clinical success and without the potential complication profile of oral medication.
  - Multifocal lesions should be treated with propranolol and followed closely.

- Angiogenesis inhibitors
  - Interferon alfa
  - Both the isoforms 2-alfa and 2-beta have been used with equal success.
  - Significant neurotoxicity in ~20% of cases (spastic diplegia) limits utility.
- Vinca alkaloids
  - Have been used with success but are not used as often in current practice

Laser Therapy

- Pulsed dye laser
  - Effective in management of capillary malformations and widely used for treatment.
  - Because depth of penetration is only ~1–2 mm, used primarily to treat cutaneous manifestations.
    - Residual telangiectasia after involution
    - Ulcerated infantile hemangioma
  - Multiple treatments might be necessary for optimization of aesthetics.
- Continuous-wave lasers
  - Argon, Nd:YAG, and potassium titanyl phosphate lasers have been used less commonly.

Surgical Management

- Surgery should be considered for complicated infantile hemangioma failing medical therapy.
  - Left untreated, it can produce permanent or undesirable sequelae.
- Facial hemangioma producing aesthetic distortion can be considered for resection.
  - These tumors impart significant caregiver and patient anxiety and distress.
  - Consideration should be given to development of the patient's facial image and self-concept.
    - These begin between 3 and 6 years of age, and peer ridicule can be problematic through the primary school-aged years.
  - For lesions producing aesthetic distortion, careful dialogue between patient, caregivers, and physician/surgeon is necessary.
- Visceral hemangioma.
  - RICH.
  - Although the lesion may be asymptomatic and require no therapy, it may be associated with high-flow shunts causing high-output cardiac failure.
  - Symptoms/signs may improve with rapid spontaneous involution or may require embolization of high-flow shunts.

WHEN TO REFER

- Early referral without delay in patients with high-risk lesions.
  - Ulceration
  - Periocular lesion
  - Airway symptoms (stridor, respiratory distress) or beard distribution
  - Perineal-lumbosacral lesion
  - Segmental (facial, perineal-lower limb)
  - Aesthetic distortion (cosmesis/deforming)
  - Multiple lesions
  - Obstruction of auditory canal
  - Uncertain diagnosis
- Otherwise, refer for optimization of final aesthetic outcome.

WHEN TO ADMIT

- High-output cardiac failure
- Airway compromise

FOLLOW-UP

- Follow patients at regular weekly/biweekly intervals early in the natural history.
  - During the proliferative phase of rapid growth a relatively innocuous appearing lesion might quickly become a high-risk lesion.
  - Low-risk lesions.
    - Regular follow-up during the proliferative phase
    - Supervisory follow-up through the involution phase
  - Patients treated with medical therapy.
    - Follow carefully to monitor progress and manage complications.

COMPLICATIONS

- Many of the common complications of infantile hemangioma involve wound care.
  - For perineal-lumbosacral lesions, frequent soiling and maceration can lead to ulceration, bleeding, and pain.
  - Parent education on meticulous wound care is paramount.
- Ulceration.
  - Risk factors include large size; segmental distribution; regions prone to friction, trauma, or maceration (perineum, lip); lesions in the proliferative phase; female gender; and preterm birth.
  - Can be caused by trauma or maceration.

- Challenging to manage; may take several weeks to heal regardless of treatment modality.
- Ulcerated infantile hemangioma is very painful.
  - Careful dressing care to avoid further trauma.
  - A topical, nonstick antimicrobial agent may help enhance wound healing.
- A small subset of hemangiomas may become infected.
  - Bacterial colonization is more common in the perineal-lumbosacral area.

- Complications of corticosteroid treatment.
  - Systemic corticosteroids.
    - Irritability
    - Cushingoid facies
    - Hypertension
    - Gastroesophageal reflux
  - Adverse effects associated with corticosteroid by injection.
    - Cutaneous atrophy
    - Telangiectasia
    - Pigmentary changes
  - Explain to parents before initiation and screen for complications while the patient is on the medication.
    - These complications resolve with discontinuation of treatment.
- Complications of β-blocker treatment.
  - Bronchospasm
  - Hypoglycemia
  - Hypotension
  - Bradycardia
  - Potentially, limb cyanosis, hyperkalemia, and seizure
    - Although the long-term effects and efficacy of propranolol in infantile hemangioma have not been established, early evidence suggests complications are less frequent than with corticosteroids.

PROGNOSIS

- Infantile hemangioma is benign but unpredictable.
- It is impossible to predict period of growth, size, complications, timing of distinct phases, and degree of involution.
- The potential exists for the development of functional complications, associated conditions, and aesthetic distortion.
- Classically, 50% of hemangiomas involute by age 5 years, 70% by age 7 years, and 90% by age 9 years.
  - These metrics are no longer considered reliable.
  - Recent evidence illustrates that ~20%–40% of patients will have residual and disfiguring skin changes.
  - Many lesions do not involute completely.

DEFINITION

- Urine that contains blood or erythrocytes
- Microscopic
  - >5 erythrocytes per high-power field seen on microscopy of centrifuged urine
- Macroscopic (or gross)
  - Red or brown (cola-colored) urine with erythrocytes seen on microscopy

HISTORY

- Hematuria may manifest as
  - Dramatic change in the color of a child's urine (often red or pink)
  - Blood on a diaper or underwear
  - Finding on urinalysis
- Hematuria of glomerular origin
  - Presents with brown-, tea-, or cola-colored urine
  - Is marked by the presence of erythrocyte casts
  - Is typically painless

Macroscopic Hematuria

- Obtain a detailed description of the urine.
  - Renal or glomerular causes of hematuria result in tea- or cola-colored urine.
  - Hematuria of lower tract origin causes red or pink urine.
  - Highly turbid urine may indicate the presence of cells.
    - Suggests glomerular disease or infection
- Blood clots suggest urinary tract bleeding.
- Timing of the bleeding may be helpful.
  - If bleeding occurs only with the onset of micturition, the source of the bleeding is likely to be in the lower tract.
- Laboratory and radiologic evaluation is dictated by associated signs and symptoms from a detailed history and physical examination.
  - Important historical elements include associated urinary symptoms, such as
    - Dysuria
    - Frequency
    - Urgency
    - Enuresis
  - A decrease in urine output should prompt particular concern and rapid evaluation and treatment.
- A review of systems should include associated symptoms.
  - Abdominal pain or colic
  - Upper respiratory infection symptoms
  - Swelling of extremities
  - Blurry vision or headaches suggestive of hypertension
- Ask patient or parents about
  - Prior episodes of hematuria
  - Preceding infections
    - Documented group A streptococcal throat infection
    - History of sore throat or skin infection
  - History of trauma
  - Other illnesses, such as the presence of sickle cell trait or sickle cell disease
- Systemic illnesses may be suggested by history of
  - Fever
  - Malaise
  - Weight loss
  - Alopecia
  - Rash
  - Joint pains (eg, as seen in rheumatologic disease)
- Important points of family history include
  - Other family members with hematuria or kidney or rheumatologic disease
  - Any history of deafness, which may occur with Alport syndrome

Microscopic Hematuria

- Recent history of throat or skin infections
- Family history of hematuria, deafness, or kidney disease

PHYSICAL EXAMINATION

- Growth parameters
- Measurement of blood pressure
- Evaluation of abdominal or costovertebral angle tenderness
- Search for evidence of local trauma to the genitourinary tract
- Inspection and palpation for periorbital, genital, or extremity edema

DIFFERENTIAL DIAGNOSIS

- Macroscopic hematuria
  - Is a common sign of glomerular and urologic disease.
    - For specific entities, see the following Microscopic hematuria section.
  - Rarely is a cause of anemia.
  - Renal or glomerular causes result in tea- or cola-colored urine.
  - With lower tract origin, urine is pink or red with or without clots.
  - Highly turbid urine may indicate the presence of cells and suggests glomerular disease or infection.

- Blood on a diaper or underwear.
  - Most commonly occurs with trauma to or manipulation of the genital area
    - In boys, localized irritation of the meatus is the most frequent cause.
    - Responds to treatment with petroleum jelly and reassurance to the parent without further evaluation.
  - Other causes include
    - Sexual abuse
    - Urinary tract infection with *Serratia marcescens*
- Hematuria in association with edema and hypertension suggests glomerulonephritis.
- Other causes include
  - Hemorrhagic cystitis
  - Trauma
  - Nephrolithiasis
  - Tumor
  - Renal vein thrombosis
  - Factitious hematuria

■ Microscopic hematuria
- Benign transient hematuria
- Thin basement membrane disease (TBMN)
  - Also called *hereditary hematuria, benign familial hematuria,* or *benign hereditary nephritis.*
  - One of the most common causes of persistent microhematuria.
  - Characterized by
    - Painless microscopic hematuria with minimal proteinuria
    - Normal renal function
  - Persistent microhematuria distinguishes TBMN from other acute renal causes of hematuria, such as postinfectious glomerulonephritis.
  - 5%–22% of affected individuals will have an episode of macroscopic hematuria associated with an infection or glomerulonephritis.
  - Renal biopsy reveals uniform thinning of the glomerular basement membrane.
  - Transmitted in an autosomal-dominant fashion.
  - Diagnosis is suggested by
    - Family history of microscopic hematuria without symptomatic renal disease
    - Asymptomatic parent testing positive for hematuria
  - No evidence has been found to support treatment of TBMN, which is typically nonprogressive.
  - Affected children should be monitored for hypertension, proteinuria, and renal insufficiency with a yearly urinalysis and blood pressure check.
    - May point to any of the following conditions, each of which has been reported in association with TBMN:
      - Immunoglobulin A (IgA) nephropathy
      - Alport syndrome
      - Nephrolithiasis
      - Glomerulonephritis
- Infection
  - Pyelonephritis
  - Cystitis
- Hypercalciuria
  - Defined as
    - Urine calcium to creatinine ratio >0.21
    - >4 mg/kg/d of excreted calcium in a 24-hour urine collection
  - Increased risk for nephrolithiasis, especially
    - In older children
    - In children with macroscopic rather than microscopic hematuria
    - With a family history of stone formation
- Sickle cell anemia or trait
- Trauma
- Exercise
- Glomerular disease
  - Postinfectious glomerulonephritis
  - IgA nephropathy
  - Henoch-Schönlein purpura
    - Common systemic vasculitis in children
    - Usually associated with
      - Crampy abdominal pain
      - Arthralgia
      - Palpable purpura
      - Can produce glomerulonephritis with hematuria
  - Systemic lupus erythematosus (SLE)
  - Focal segmental glomerulosclerosis
  - Membranoproliferative glomerulonephritis
  - Alport syndrome
    - Genetic disorder
    - Risk for sensorineural hearing loss and eye abnormalities
- Congenital abnormality
  - Ureteropelvic junction obstruction
  - Cystic disease
- Vascular malformation
- Drugs or toxins

- Mistaken "hematuria" (urinalysis with <5 red blood cells)
  - Myoglobinuria
  - Hemoglobinuria
  - Urine discolored by
    - Beets
    - Blackberries
    - Ibuprofen
    - Rifampin
    - Nitrofurantoin

LABORATORY EVALUATION

- Most children with isolated microscopic hematuria do not have a serious or treatable cause for the hematuria and do not require an extensive workup.
  - If child is asymptomatic and normotensive, repeating urinalysis at least once before further evaluation is prudent.
  - Persistent microhematuria may represent the early presentation of a progressive glomerular disease.
    - IgA nephropathy
    - Alport syndrome
- Begin with urinalysis with microscopic examination of fresh-spun urine sample to confirm the presence of erythrocytes.
  - Dysmorphic erythrocytes and erythrocyte casts are pathognomonic of hematuria of glomerular origin.
  - With <5 erythrocytes on microscopy, not hematuria.
- Nephrolithiasis may be suggested by the presence in urine of
  - Calcium
  - Uric acid
  - Cystine crystals
- Infectious causes of hematuria are indicated by
  - Leukocyte casts
  - Leukocyte esterase
  - Nitrate positivity on urine dipstick
- Urine culture should be performed on
  - All patients with urinary symptoms
  - Infants with unexplained fever or sepsis
- Further evaluation is determined by the most likely cause of the blood in the urine.
  - With suspected glomerular disease
    - Serum electrolytes
    - Blood urea nitrogen
    - Creatinine
    - Calcium and phosphorus
    - Liver function tests if there is a nephrotic component
  - To help determine the cause of glomerulonephritis
    - Antinuclear antibodies
    - Complement studies (C3, C4, total complement)
    - Streptozyme and streptolysin O antibody titers
- Patients with a history of sore throat should undergo
  - Throat culture
  - Rapid testing for group A β-hemolytic streptococci

IMAGING

- Every child with macroscopic hematuria should have renal ultrasonography to rule out
  - Nephrolithiasis
  - Tumor
  - Urologic abnormalities
    - Cystic disease
    - Obstructive uropathy
    - Parenchymal renal disease
- A renal Doppler study is needed to evaluate for suspected vascular thrombosis, renal infarcts, or renal artery stenosis.

DIAGNOSTIC PROCEDURES

- Renal biopsy may be performed for
  - Family history of hematuria
  - History or laboratory evaluation suggestive of rheumatologic disease, such as SLE
- Renal biopsy is absolutely indicated in cases of hematuria with
  - Nephrotic syndrome
  - Recurrent hematuria
  - Azotemia
  - Renal insufficiency

TREATMENT APPROACH

- Management of glomerular disease depends on the cause of the glomerulonephritis.
- Poststreptococcal glomerulonephritis.
  - Low C3 levels and elevated streptolysin O antibody titers are characteristic.
  - Typically self-limited.
  - Good prognosis for long-term renal function.
- Microhematuria without any other signs and symptoms.
  - Often is benign
  - Resolves spontaneously in many cases (transient hematuria)
- School-aged children with microscopic hematuria may be observed for ≥2 years before more extensive testing is undertaken.

- Patients with glomerulonephritis need to be monitored for hypertension and, if present, need to be treated with antihypertensive medications.

SPECIFIC TREATMENT

- Treat urinary tract infections with an appropriate antimicrobial regimen.
- Skin or throat streptococcal infections should be treated with penicillin.

WHEN TO REFER

- Hematuria associated with pain.
- Persistent microscopic hematuria with
  - Associated proteinuria
  - Hypertension
  - Hearing loss
  - Family history of renal disease or deafness
- Glomerulonephritis.
  - Some types require management by a nephrologist.
- Urologic evaluation, which may include direct visualization by cystoscopy, may be required for
  - Trauma
  - Tumors
  - Cystic disease
  - Congenital obstruction
  - Hemorrhagic cystitis
  - Lower urinary tract bleeding
  - Nephrolithiasis
- Children with nephrolithiasis benefit from nephrotic and urologic evaluation.
- A family history of deafness or kidney disease and the presence of hypertension, proteinuria, or edema.
- Significant proteinuria.
- Occurrence of macroscopic hematuria.

WHEN TO ADMIT

- When hematuria (with or without proteinuria) is associated with
  - Severe abdominal or flank pain
  - Congestive heart failure or fluid overload indicative of oliguria or anuria
  - Hypertension
  - Renal insufficiency
  - Anasarca (generalized edema)

FOLLOW-UP

- Monitor growth (height).
- Monitor for hypertension.
- Hematuria should be monitored by periodic urine analysis.
- Kidney function (serum blood urea nitrogen, creatinine) may need to be monitored as appropriate.

COMPLICATIONS

- Some renal disorders associated with hematuria may lead to
  - Hypertension
  - Progressive kidney disease leading to renal failure

PROGNOSIS

- Proteinuria is a more important prognostic finding than macroscopic hematuria.
- Proteinuria and hypertension are poor prognostic indicators.

Hemoglobinopathies and Sickle Cell Disease

DEFINITION

- The normal hemoglobins (Hb) are adult hemoglobin (HbA; 96% of the total content), fetal hemoglobin (HbF; 1%), and hemoglobin A_2 (HbA_2; 3%).
- Hb synthesis is directed by controlling genes that are switched on and off at certain stages of human life, resulting in different globin-chain synthesis at different times.
- Inherited Hb disorders due to single-gene defects include
  - Thalassemias: structurally normal but decreased amounts of globin chains
    - — α-Thalassemias
    - — β-Thalassemias
  - Structural Hb abnormalities: abnormal globin chains
    - — Sickling disorders
    - — Sickle cell trait
      - Benign carrier state
    - — Rare structural hemoglobinopathies

SIGNS AND SYMPTOMS

- α-Thalassemia
  - Silent carrier
    - — No anemia
  - HbH disease
    - — Hemolytic anemia of variable severity and splenomegaly.
    - — A serious drop in Hb can occur with infections or ingestion of substances that induce oxidant stress.
  - Hb Bart disease
    - — Severe anemia
  - ATR-X syndrome: α-thalassemia seen in nontropical populations
    - — Severe intellectual disability
    - — Minor facial anomalies
    - — Genital anomalies
    - — Mild form of HbH disease
- β-Thalassemia
  - Clinical presentation is variable.
  - Thalassemia major.
    - — Symptoms at ~6 months with anemia that can be severe and symptomatic.
    - — Growth failure.
    - — Cardiac dysfunction.
    - — Pallor.
    - — Jaundice.
    - — Hepatosplenomegaly.
    - — The patient's body becomes loaded with iron, even when transfusions are sparingly provided.
      - Liver effects (leading to cirrhosis)
      - Pituitary effects (leading to hypogonadism and growth failure)
      - Heart effects (leading to arrhythmia and cardiomyopathy)
      - Bone effects (leading to pathologic fractures)
  - Thalassemia intermedia.
    - — Patients exhibit symptoms later in life.
    - — Anemia is well compensated.
      - May be exacerbated by infection, folate deficiency, or increasing hypersplenism
- Sickling disorders
  - Pallor.
  - Jaundice.
  - Increased fatigue.
  - Gallstones.
  - Poor growth.
  - Aplastic crises occur
    - — After viral infections (most commonly parvovirus B19)
    - — In situations in which transient marrow suppression results in a life-threatening decrease in Hb
  - Episodic, variable, and unpredictable musculoskeletal pain.
    - — Disabling if frequent and severe
    - — Usually uncomplicated and not life-threatening
  - Acute bone pain or infarction.
    - — Common at all ages
  - Dactylitis (foot and hand swelling) is a classic early childhood symptom.
  - Splenic sequestration crisis may occur.
    - — Sudden pooling of blood in the spleen with hypovolemic shock
    - — Life-threatening and recurrent syndrome of early childhood
  - Strokes, although uncommon, are a recurrent and serious problem.
  - Variety of cerebrovascular catastrophes, such as hemorrhage and thrombosis, can occur.
  - Acute chest syndrome is common.
    - — Pulmonary infarction or pneumonia (or both)

- Large volumes of dilute urine even in young children.
  - Need copious fluid intake to avoid dehydration
- Hematuria.
- Priapism.
- Trophic leg ulcers.
- Blindness.

- Sickle cell trait
  - The heterozygous state resulting in HbS trait (AS pattern).
  - Most people have no clinical symptoms.
  - Can cause hematuria and a loss of urine-concentration capacity.
  - Symptoms from intravascular sickling have been reported with
    - Complications during strenuous exercise with dehydration or at high altitudes
    - Flying at high altitudes in unpressurized aircraft
  - However, HbS β^0-thalassemia is a double heterozygous condition that results in a disease as severe as HbSS disease.
- High oxygen-affinity Hb
  - High arterial oxygen saturation
  - Markedly left-shifted oxygen-dissociation curve
  - Presence of familial erythrocytosis (polycythemia)
- HbM
  - History of cyanosis since birth, with a normal oxygen saturation
- Low oxygen-affinity Hb
  - Right-shifted oxygen-dissociation curve

DIAGNOSTIC APPROACH

- High-performance liquid chromatography has become the test of choice for the diagnosis of thalassemias and hemoglobinopathies because it reliably separates Hb types.
- Prenatal diagnosis.
  - Specific tests, such as
    - Globin chain synthesis ratios
    - DNA analysis by sampling of fetal blood or chorionic villus
    - Restriction fragment polymorphism
- α-Thalassemias.
  - Confirmation of decreased α chains by globin-chain synthesis measured in reticulocytes
    - Expensive and hard to do
- Sickling disorders.
  - Clinical history and physical findings are the first steps to diagnosis.
  - In most developed countries, including the United States, the diagnosis of sickle cell disease is established through newborn screening.
    - Hb separated from dried blood spots collected from neonates in the newborn nursery allows for identification of affected neonates before the onset of clinical manifestations.
  - Clinical history and physical examination are the first steps in older patients in whom the diagnosis of sickle cell disease is suspected and who were born before the initiation of the newborn screening program or outside the United States.

LABORATORY FINDINGS

Thalassemias

- Usually associated with
  - A low mean cell volume (microcytosis)
  - Normal or near-normal mean cell Hb concentration
  - Increased or normal red blood cell (RBC) count
  - Normal or decreased Hb concentration
- Iron deficiency can present with similar indices, with the exception of the RBC count that is low (not increased or normal).
- Iron deficiency should be excluded before evaluation for thalassemia trait.
  - If iron studies are normal, an Hb evaluation or electrophoresis should be obtained to evaluate for increased HbA_2 and HbF.
  - Hb electrophoresis will also demonstrate structurally abnormal Hb, such as HbC, HbS, or HbE.
- α-Thalassemias.
  - Routine complete blood cell count shows hypochromia (mean cell Hb <27 pg).
  - Microcytosis (mean cell volume <80 fL).
  - Mild anemia with normal HbA_2.
  - Abnormal Hb tetramers are demonstrated by
    - Presence of RBC inclusions on cresyl blue stain
    - Hb electrophoresis
    - Rapid movement (faster than HbA)
      - Require special attention during electrophoresis testing
  - Hb Bart (γ-tetramers) are found in the first few weeks of life, and HbH can be found in older patients.
  - Silent carrier: normal RBC count.
  - HbH disease: fragmented cells with hypochromia and microcytosis.

H

- β-Thalassemia: thalassemia major.
  - RBCs may be destroyed within the marrow, leading to ineffective erythropoiesis.
    - Hallmark of β-thalassemia
  - Decreased Hb content per cell.
  - Hypochromia.
  - Microcytosis.

Structural Hemoglobinopathies

- Sickling disorders.
  - Morphologic sickling can be assessed by blood smears.
  - Presence of HbS is evaluated by the solubility test.
    - Inexpensive and sensitive to the carrier state
    - Does not distinguish trait from the disease
  - Hb electrophoresis confirms the exact phenotype.
  - In most developed countries, including the United States, the diagnosis of sickle cell disease is established through the newborn screening program.
    - Hb is separated from dried blood spots collected from neonates in the newborn nursery and allows for early identification of affected neonates before the onset of clinical manifestations.
  - In older patients in whom the diagnosis of sickle cell disease is suspected, clinical history and physical examination are the first steps to diagnosing a sickling disorder.
  - Blood smears are used to assess
    - The presence of hemolytic anemia (low Hb, high reticulocyte counts, increased bilirubin, and lactic dehydrogenase)
    - Morphologic sickling
- Unstable Hb.
  - Hemolytic anemia.
  - Detection of Heinz bodies by staining and heat precipitation test.
  - Hb electrophoresis is not always useful because of the tendency of Hb to rapidly denature.
- High oxygen-affinity Hb.
  - High RBC mass
- Low oxygen-affinity Hb.
  - Hb level and RBC mass are normal.
- HbM.
  - Brown discoloration of freshly drawn blood.
    - Does not change with aeration
  - Spectrophotometry confirms presence of methemoglobin.
  - Electrophoresis demonstrates abnormal Hb.
- A prenatal diagnosis of a clinically important hemoglobinopathy can be made by DNA analysis on sampling of fetal blood or the chorionic villus.

IMAGING

- Transcranial Doppler (TCD)
  - Elevated time-averaged mean velocity in the middle cerebral and distal internal carotid arteries on screening.
  - TCD has been shown to be associated with a high risk for overt stroke in patients with HbSS.
  - TCD screening and chronic blood transfusions for abnormal TCD results are now recommended.

DIAGNOSTIC PROCEDURES

- Hb electrophoresis may be diagnostic in many hemoglobinopathies and thalassemias.

CLASSIFICATION

- See **Table 1.**

TREATMENT APPROACH

- Blood transfusion.
  - Continues to be the mainstay of care of patients with hemoglobinopathies.
  - Transfusion safety is an important consideration, particularly prevention of transfusion-transmitted infections.
    - Donors should be screened for hepatitis B and C, HIV, syphilis, and malaria.
    - Donor screening may sometimes be ineffective.
      - Insensitive tests
      - Expired kits and reagents
      - Improper procedures
- Iron chelation.
  - Deferoxamine.
    - Daily 8-hour subcutaneous infusion via small portable pumps
    - Well tolerated and extremely effective
  - Oral deferasirox.
    - Similar efficacy as deferoxamine in preclinical trials and much less cumbersome for patients.
    - Starting dose is 20 mg/kg once daily as a dispersion in water or orange or apple juice.
    - Highest recommended dose is 30 mg/kg/d.

Table 1. Classification of the α-Thalassemias

Phenotype	Number of α Genes	α/β Synthetic Ratio	Haplotype	Genotype	Clinical Features
Normal	4	1.0	α, α	αα/αα	None
Silent carrier	3	0.8	α^+, α	–α/αα	No anemia, normal RBC count
2-Gene deletion (α-thalassemia 1)	2	0.6	α^0, α or α^+, α^+	– –/αα or –α/–α	Mild anemia, hypochromia, and microcytosis
HbH disease	1	0.3	α^0, α^+	– –/–α	Moderate anemia, fragmented cells with hypochromia and microcytosis
Fetal hydrops	0	0	α^0, α^0	– –/– –	Death in utero caused by severe anemia

Abbreviations: α^0, no normal α-globin; α^+, globin is reduced; Hb, hemoglobin; RBC, red blood cell.

- Toxicities.
  - Increase over baseline of creatinine and proteinuria
    - Pediatric patients with sickle cell disease have low creatinine concentration.
      - ▶ Increases of 30% over baseline should prompt dose decreases.
  - Chemical hepatitis or aminotransferase elevation over baseline
    - Usually respond to dose decreases to 10 mg/kg/d
- Treatment effectiveness is measured by monitoring serum ferritin level.
  - Not the most accurate measure of total body iron stores.
  - Levels <2,500 mg/dL are associated with improved cardiac disease–free survival.
  - Chelation should be interrupted for serum ferritin levels ≤500 ng/mL because of increased drug toxicity at low ferritin levels.
  - Magnetic susceptometry provides a noninvasive method for measuring hepatic iron stores.
    - This test is available in only a few centers worldwide.

■ Stem cell transplantation.
- Improved techniques that use human leukocyte antigen (HLA)-matched sibling donors may result in cures for hemoglobinopathies.
- Interest exists in nonmyeloablative or reduced-intensity myeloablative stem cell transplantation.
  - Has reduced morbidity but leads to a chimerism in the recipient.
  - This procedure is still investigational.

■ Advances in genomics and other technologies.
- Promise to improve treatment of patients with hemoglobinopathies

■ Recent development of successful intrauterine diagnosis of 4 gene deletions has allowed intrauterine blood transfusions of the fetus, and viable births have been possible.

SPECIFIC TREATMENTS

β-Thalassemia

■ Blood transfusions are provided to
- Correct anemia.
- Suppress erythropoiesis.
- Prevent growth failure.
- Inhibit increased gastrointestinal absorption of iron.

■ Splenectomy
- Usually performed if transfusion requirements increase because of hypersplenism

■ Folic acid supplementation
- May be considered to meet its increased requirement

■ Iron chelation

- Hematopoietic stem cell transplantation
  - May be performed when chronic transfusions and chelation are not possible
    - If successful, reverses need for transfusions or chelation therapy.
    - Risk of serious adverse effects.
      - Graft failure
      - Rejection
      - Graft-versus-host disease
      - Death
    - Does not reverse preexisting and established growth failure, endocrinopathies, and gonadal dysfunction.
    - Must also consider availability of supportive care after transplantation.
    - Using related or unrelated HLA-matched donors results in excellent outcomes in low-risk patients without extensive organ damage.

Structural Hemoglobinopathies

Sickling Disorders

- Give symptomatic and supportive care of complications.
  - Treat pain episodes with analgesics (often narcotics) and local heat packs.
  - Ensure adequate hydration.
  - Adjust acid-base balance.
  - Prevent hypoxia.
  - Avoid exposure to cold.
  - Treat febrile episodes early and aggressively with antibiotics.
- Judicious use of blood transfusions will help
  - Prevent strokes.
  - Correct severe anemia (Hb level <5 g/dL, usually with aplastic crisis or splenic sequestration).
- Management is optimized by early diagnosis with screening of newborns.
- Routine daily prophylactic penicillin and pneumococcal vaccine.
  - To prevent high childhood mortality from infections
- Agents that stimulate HbF production (eg, hydroxyurea) may be administered.
- Peripheral or cord blood stem cell transplantation from an HLA-identical sibling.
  - High-risk procedure
  - Can be curative
  - Used for certain individuals with markers for adverse outcome (eg, stroke in a young child)
- Future directions.
  - Anti-sickling agents, such as membrane-active drugs
  - Gene therapy
- Preoperative blood transfusion for invasive surgery with prolonged anesthesia is useful to avoid intraoperative and postoperative complications.

Rare Structural Hemoglobinopathies

- Unstable Hb
  - Avoid oxidant drugs.
  - Provide transfusions as clinically indicated.
  - Remove the spleen if anemia is severe.
- High oxygen-affinity Hb
  - Maintain hematocrit at 70% by phlebotomy to prevent high viscosity.
- Low oxygen-affinity Hb
  - No specific management is necessary or effective.
  - Cyanosis is relatively well tolerated if strenuous activities are avoided.
- HbM
  - No management is needed; the amount of HbM is insufficient to cause physiologic derangements.

WHEN TO ADMIT

- Anemic crisis (Hb level <5 g/dL or hemodynamic compromise)
- Sudden splenic enlargement
- Pain not responding to home opioids
- Difficulty in breathing, chest pain
- High fever spikes (>38.0°C [100.4°F] core, repeated in 30 minutes)
- Any central nervous system symptoms

WHEN TO REFER

- All patients with thalassemia intermedia and thalassemia major should be followed by a hematologist.
- All children with sickle hemoglobinopathies, regardless of whether the child has experienced serious complications of sickle cell disease, should be regularly followed by a hematologist.
- Referral should occur immediately after a positive newborn screening result is returned.
- Serious complications can include stroke, splenic sequestration, and recurrent acute chest syndrome.
- Pregnant patients should be referred for care during pregnancy.

FOLLOW-UP

- Patients with thalassemia major require regular transfusions for survival.
- Monitoring for chelation regimens.
  - Annual audiologic and ophthalmologic examinations
  - Annual echocardiographic examinations

COMPLICATIONS

- Beginning in early childhood, risk of severe bacterial infections is lifelong.
  - Common cause of death
- Transfusion-transmitted infections remain a risk.
- Hb Bart disease
  - Invariably results in death in utero or shortly after birth due to severe anemia
  - Is associated with life-threatening complications to the mother
    - Placentomegaly
    - Hypertension and preeclampsia
    - Disseminated intravascular coagulation
    - Hemorrhage
- HbH disease.
  - A serious decrease in Hb can occur with infections or with ingestion of substances that induce oxidant stress.
  - Fetal hydrops
    - Devastating complication associated with nondeletional forms of HbH disease
    - Associated with similar fetal and maternal complications as Hb Bart fetal hydrops, including death in utero

PROGNOSIS

- Sickling disorders
  - Disease is extremely variable in severity.
  - Factors that affect disease severity include
    - Presence of genetic markers, such as the β-gene haplotype
    - Co-inheritance of α-thalassemia (beneficial)
    - Amount/distribution of HbF (Higher levels are beneficial.)
- Hb Bart disease
  - Invariably results in death in utero or shortly after birth due to severe anemia

PREVENTION

- Simple awareness of genetic diseases and education and counseling of families at risk
  - Low-tech but crucial in avoiding burden of these diseases to individuals and society
- The primary reason to screen patients for hemoglobinopathy is to identify risk of producing offspring with clinically important disease, such as
  - β-Thalassemia major
  - Sickle cell disease
  - Severe α-thalassemia (fetal hydrops)
- Screening of parents
  - Complete blood cell count while paying attention to RBC indices
    - Thalassemias are usually associated with
      - Low mean cell volume (microcytosis).
      - Normal or near-normal mean cell Hb concentration.
      - Hb concentration may be decreased or normal with a high RBC count.
  - Once iron deficiency is ruled out and hemoglobinopathy is suspected
    - Perform Hb electrophoresis evaluation for levels of HbA_2 and HbF and presence of an abnormal Hb, such as HbC, HbS, or HbE.
  - Premarital screening and genetic counseling
    - Easy and inexpensive.
    - Good ways to provide reproductive options for couples at risk for children with hemoglobinopathies.
    - Nondirective genetic counseling should be provided and targeted to populations with a high prevalence of the hemoglobinopathy traits.
- Prenatal diagnosis
  - Specific tests, such as globin-chain synthesis ratios or DNA analysis by sampling fetal blood or chorionic villus
  - Chorionic villus sampling
    - Challenges include technical difficulties and expense.
    - Women with at-risk pregnancies must be assessed for prenatal diagnosis, ideally in the first trimester (8–14 weeks' gestation).
    - Choice of therapeutic abortion for involved pregnancies can be difficult, depending on cultural and religious beliefs.
    - Research studies report a higher acceptance of prenatal diagnosis if another child is affected.
  - Preconception diagnosis and implantation of normal embryos after in vitro fertilization
    - Extremely expensive alternative
    - Currently available in the West
  - In utero therapy that uses stem cell transplantation
    - Would help at-risk couples who do not opt for termination
    - Currently in early trials

Hemolytic Uremic Syndrome

DEFINITION

- Hemolytic uremic syndrome (HUS) is a systemic thrombotic microangiopathy (TMA) characterized by the classic triad of
  - Microangiopathic hemolytic anemia (MAHA)
  - Thrombocytopenia
  - Acute kidney injury
- The kidney is the most common and clinically significant site of injury.
- Multiple other organ systems can be affected, including
  - Central nervous system (CNS)
  - Gastrointestinal tract
  - Heart
  - Lungs
  - Pancreas
- HUS is broadly categorized into 2 types.
  - Typical or D+ HUS follows diarrheal illness or is related to specific infectious agents.
    - Most common type.
    - Most cases are related to infection by Shiga toxin-producing enterohemorrhagic *Escherichia coli*.
    - Tends to be self-limited and less severe than genetic forms.
  - Atypical HUS (aHUS) is most commonly caused by genetic mutations in the complement cascade.
    - A longer, potentially recurrent course
    - More commonly leads to chronic kidney disease

SIGNS AND SYMPTOMS

- Typically starts with the development of watery diarrhea following an incubation period of 3–8 days.
- 50% of patients then develop bloody diarrhea, abdominal cramping, and nausea and vomiting.
- Fever is present in ~30% of patients.
- These symptoms precede more systemic symptoms, which include
  - Malaise
  - Pallor
  - Renal manifestations, marked by the development of acute kidney injury
- Hypertension.
  - Result of fluid retention and edema in the acute phase
  - Develops in ~50% of children with HUS
  - May persist as chronic hypertension in the long term
- ≤30% of patients can have CNS involvement manifesting as lethargy, seizures, and, sometimes, cerebral edema and coma.

DIFFERENTIAL DIAGNOSIS

- Differential diagnosis of HUS is wide and includes
  - Acute poststreptococcal glomerulonephritis
  - Thrombotic thrombocytopenic purpura (TTP)
  - Systemic lupus erythematosus
  - Henoch-Schönlein purpura
  - Disseminated intravascular coagulation
  - Sepsis
  - Intussusception
  - Renal vein thrombosis
    - Can be discerned by renal ultrasound, typically with unilateral renal enlargement compared to HUS, in which both kidneys are enlarged
- Thrombotic microangiopathies fall along a spectrum, and there can be overlap between HUS and TTP.
  - TTP is defined by the 3 criteria of HUS (MAHA, thrombocytopenia, and acute kidney injury) *plus* neurologic signs and fever.
  - Renal impairment usually is not the prominent feature in TTP.
- A major distinguishing feature of HUS and TTP compared with the other entities in the differential diagnosis is the presence of schistocytes on the peripheral blood smear.

DIAGNOSTIC APPROACH

- The clinical outcome and short- and long-term treatment vary greatly depending on the cause.

LABORATORY FINDINGS

- Laboratory studies reflect the underlying pathology of HUS and show
  - Anemia
  - Thrombocytopenia
  - High levels of lactate dehydrogenase
  - Low haptoglobin
  - Fragmented erythrocytes (schistocytes) on peripheral blood smear
- The onset of renal involvement is evidenced by
  - Hematuria
  - Red blood cell casts on urine microscopy
  - Proteinuria
  - Elevated serum creatinine
- Other laboratory abnormalities reflect damage to extrarenal organs.
  - Elevated pancreatic enzymes
  - Elevated troponin levels

IMAGING

- Renal ultrasonography
  - In HUS, there is symmetric enlargement of both kidneys.
  - In renal vein thrombosis, unilateral renal enlargement is typical.

TREATMENT APPROACH

- Management is similar to the therapy for children with acute kidney injury from other causes, with additional attention to issues specific to HUS.
  - The approach to the electrolyte, acid-base, and volume overload associated with HUS is based on medical management.
  - In addition to aggressive management of the renal sequelae of HUS, specific attention must be paid to other affected organ systems.
- Two-thirds of children with HUS require acute dialysis.

SPECIFIC TREATMENTS

Volume Management

- Strict attention to volume management is required.
  - Initial fluid resuscitation may be necessary.
  - Fluid overload can occur, particularly in critically ill patients.
- Patients without anuria can be treated early with loop diuretics.
- For patients with anuria
  - Acute dialysis with hemodialysis, peritoneal dialysis, or continuous renal replacement therapy has contributed to reduced mortality rate, from ≤50% to 3%–5%.

Antibiotics and Antimotility Agents

- The use of antibiotics to treat typical HUS is controversial.
  - Some studies have shown benefit from the use of antibiotics; several others have demonstrated not only lack of benefit but also a potential for harm.
  - No clear benefit has been demonstrated for the use of antibiotics in patients in the acute phase of HUS, and their use is not currently recommended.
- Antimotility agents are contraindicated in patients with HUS.
  - Although helpful with the symptomatic treatment of diarrhea, their use increases the risk of developing toxic megacolon in the setting of typical HUS.

Plasma Exchange

- Typical HUS.
  - Evidence for the use of plasma exchange has not been definitive, but some data support plasma infusion or plasma exchange in this setting.
  - Plasma therapy should be considered for children who have a significant worsening of disease.
    - Severe renal failure
    - Heart failure
    - Neurologic symptoms
  - Plasma therapy is contraindicated in patients with HUS associated with *Streptococcus pneumoniae.*
    - The presence of preformed antibodies to the Thomsen-Friedreich antigen in plasma can worsen the disease process.
- aHUS.
  - Response to plasma therapy may vary depending on the underlying mutation causing the disease.
  - Overall, the use of plasma exchange in patients with aHUS has been shown to decrease mortality.
  - Suggested regimen.
    - Initiation of plasma exchange within 24 hours of disease onset
    - Exchange of 1–2 volumes/d or infusion of ~20–30 mL/kg body weight
  - Decisions about initiation and continuation of plasma therapy should be made following consultation with a pediatric subspecialist experienced with aHUS.
- TMAs.
  - There can be overlap between HUS and TTP.
- Patients rarely require dialysis.
- For patients with TTP presenting with severe multisystem failure, plasma exchange should be initiated early.

Eculizumab

- Treatment with eculizumab, an anti-C5 monoclonal antibody, has recently shown benefit in the treatment of aHUS.
- Reports demonstrated termination of the microangiopathic process.
  - Some variability exists with respect to prevention of long-term consequences of HUS, including the improvement in renal function.
- A recently published report of phase 2 trials of eculizumab in a more chronic setting showed improvement in estimated glomerular filtration rate over the course of the trial, with earlier use showing the most significant result.

- The risk of meningococcal infection is increased in patients taking eculizumab.
  - These patients should receive meningococcal vaccination before or as soon as possible after starting treatment.
  - They also should receive antibiotic prophylaxis against meningococcal infection.

Blood Products

- The hematologic effects of HUS should be managed cautiously.
  - Close attention must be given to development of volume overload and pulmonary edema.
- Packed red blood cell infusions should be limited to cases when
  - The hemoglobin is rapidly down trending *or*
  - The patient shows clinical changes related to anemia.
- Treatment of thrombocytopenia should also be limited because it may worsen the development of microthrombi.
- Indications for platelet transfusion.
  - Active bleeding
  - Need for surgical procedures
- Diuretic therapy should be used in conjunction with blood product infusions to prevent volume overload.

Kidney Transplantation After HUS

- Typical HUS
  - Children who progress to end-stage renal disease following typical HUS are not at increased risk of graft failure compared with patients without HUS.
- aHUS
  - Children with HUS related to genetic mutations have a high rate of HUS recurrence in the kidney graft—≤60% in one study.
    - An adult HUS study demonstrated that this recurrence is an independent risk factor for graft loss.
  - The risk of HUS recurrence and graft loss can vary depending on the underlying genetic defect.
    - Defects in membrane-bound proteins, such as membrane cofactor protein (MCP), tend to have a lower risk of HUS recurrence in transplanted kidney compared with those with circulating factor defects (eg, complement factor H, complement factor I).
    - A subset of patients with defective MCP can have combined errors in MCP and circulating factors.
  - Kidney transplantation in aHUS should be a case-by-case consideration rather than an absolute contraindication.
  - Plasma therapy and eculizumab have shown some success in reducing the risk of posttransplant recurrence.

WHEN TO ADMIT

- All patients with HUS must be admitted.

WHEN TO REFER

- All patients with HUS should be referred to a nephrologist and other subspecialist as indicated.

FOLLOW-UP

- The likelihood of long-term renal dysfunction is high.
- Children should receive regular follow-up with a nephrologist to monitor parameters such as
  - Hypertension
  - Proteinuria
  - Growth
  - Progression of chronic kidney disease
- The treatment of hypertension and proteinuria with angiotensin-converting enzyme inhibitors is prudent to reduce further worsening of renal damage in the chronic setting.

COMPLICATIONS

- With better survival rates during the acute phase of HUS, long-term sequelae have become clearer.
- One study of 61 children showed that following acute HUS, 39% had a risk of long-term complications.
- A meta-analysis showed
  - Death or end-stage renal disease in 12% of children with typical HUS.
  - 25% of survivors had some long-term renal complications.
- The duration of oligoanuria is a predictor of the occurrence of late complications following HUS.

PROGNOSIS

- Mortality rates in patients with typical HUS is now between 3% and 5%.
  - Typically seen in cases with more severe and widespread effects on multiple organ systems
- Survival rates during the acute phase of HUS have improved.

- Long-term sequelae may include
  - Hypertension
  - Proteinuria
  - Chronic or end-stage renal disease
  - Long-term renal complications
  - Glomerulosclerosis
  - Interstitial fibrosis

PREVENTION

- Properly cooking meats and good hygiene will prevent infections with organisms associated with HUS and thus prevent D+ HUS.

Hemoptysis

DEFINITION

- Hemoptysis is spitting or coughing of blood that originates within the thorax.
- Presentation ranges from flecks of blood in the sputum to massive bleeding that can lead to respiratory distress or death.

HISTORY

- Four important considerations should be kept in mind in evaluating children with hemoptysis.
  - Whether the bleeding requires an emergency resuscitative effort.
  - Whether what appears to be hemoptysis is bleeding from the upper airway or gastrointestinal tract.
    - The source of the bleeding should be established.
  - Children with lower respiratory tract infection but no chronic disease usually
    - Have mild, self-limited bleeding.
    - Require no specific treatment other than management of the underlying acute illness.
  - Management of hemoptysis that arises from a localized site differs from that which causes a diffuse alveolar hemorrhage, which may be the presenting sign of an underlying immunologic disorder.
- A detailed history of pulmonary and non-pulmonary symptoms often permits a tentative diagnosis.
- The presumptive diagnosis can then be proved or disproved by findings on physical examination and specific laboratory tests and procedures.
- Aspects of the history that help focus the evaluation include
  - Recent trauma.
  - Easy bruising.
  - Family history of bleeding disorders.
  - Menstrual irregularities.
  - Pleuritic chest pain.
  - Fever.
  - Weight loss.
  - Arthralgias.
  - Changes in urine color.
  - Previous heart disease or surgery.
  - Surgical procedures.
  - Medication use.
  - Substance abuse.
  - Pica.
  - Asthma not responsive to appropriate medical therapy.
  - Travel to or from developing countries and areas that raise sheep may necessitate evaluation for mycobacterial, mycotic, or parasitic lung infections.
- Recurrent pneumonitis, sinus infections, and chronic sputum production may be indicative of
  - Bronchiectasis from cystic fibrosis (CF)
  - Foreign body aspiration
  - Ciliary dyskinesia
  - Immunodeficiency disorders
  - Other chronic lung diseases

PHYSICAL EXAMINATION

- Physical examination begins with the vital signs to determine the speed at which the examination should be conducted.
- Thorough inspection of the nasal passages and oropharynx is done to rule out a non-pulmonary cause of the hemoptysis.
- As the examination proceeds caudally, certain findings on inspection and auscultation may suggest a specific diagnosis.
  - Cutaneous telangiectases and a murmur or bruit over the lung fields suggest hereditary hemorrhagic telangiectasia (Rendu-Osler-Weber syndrome).
  - Clubbing with or without adventitial breath sounds suggests bronchiectasis.
  - A saddle nose and stridor suggestive of subglottic stenosis are often seen in patients with necrotizing granulomatous vasculitis.
  - A pleuritic rub, acute pleuritic chest pain, and history of oral contraceptive use or recent abortion suggest a pulmonary embolic event or other pleural-based lesion.
  - Localized homophonous wheezing over a major airway or decreased breath sounds, with or without a cough, suggests an intraluminal obstruction, such as an aspirated foreign body.
- Evidence of trauma to the thorax may be subtle.
  - 30% of children who experience major trauma to other organ systems will be found to have thoracic trauma as well.
- Examination of the heart may provide evidence of pulmonary hypertension or a new murmur.
- Lymphadenopathy and hepatosplenomegaly raise the possibility of a lymphoproliferative disease with an associated bleeding diathesis.

DIFFERENTIAL DIAGNOSIS

No Preexisting Medical Condition

- For a child or an adolescent without a preexisting medical condition who has a first episode of hemoptysis, the most common causes are
  - Acute infectious pneumonia
  - Foreign body aspiration
- Classically, a child with pneumococcal pneumonia and hemoptysis who is old enough to expectorate
  - Is febrile
  - Appears ill
  - Has a cough that is productive of rusty sputum
- Certain other bacterial and viral lower respiratory tract infections can cause hemoptysis.
  - In these cases, hemoptysis usually
    - Occurs early in the course of the illness
    - Is self-limited
    - Consists of only blood-tinged sputum
  - Globally, the most common causes of hemoptysis in children probably are
    - Tuberculosis
      - Pulmonary tuberculosis causing hemoptysis is usually accompanied by the systemic manifestations of anorexia and weight loss.
      - Purified protein derivative testing may be negative.
    - Echinococcus
    - Paragonimiasis
- Foreign body aspiration.
  - In many cases of aspiration, the initial choking episode is not observed or not remembered.
  - Only 40% of children with foreign body aspiration exhibit the classic triad of wheezing, cough, and decreased breath sounds distal to the obstruction.
  - A bout of paroxysmal coughing may occur after the initial event, but as cough receptors in the bronchi or trachea adapt, coughing will stop.
  - Over time, and depending on the location and composition of the foreign object, subsequent inflammation will develop.
    - May result in airway obstruction, with wheezing or recurrent pneumonitis
  - If neovascularization of granulation tissue in the airways occurs, or if bronchiectasis develops, hemoptysis can occur weeks to months after the initial event.
- Autoimmune disorder or other immunologic abnormality, although rare as a presenting symptom.
  - More common in girls
  - Rarely produces hemoptysis alone
  - More commonly characterized by systemic manifestations, including (in addition to the hemoptysis)
    - Fever
    - Weight loss
    - Malaise
    - Anorexia
    - Amenorrhea
    - Rashes
    - Hypertension
- Diffuse pulmonary hemorrhage.
  - May be divided into 4 categories, all rare
    - Hemorrhage associated with antiglomerular basement membrane antibodies in serum or tissue (eg, Goodpasture syndrome)
    - Hemorrhage associated with an autoimmune-mediated disease (eg, systemic lupus erythematosus)
    - No immunologic abnormalities but presence of antibodies to cow's milk (Heiner syndrome)
      - Pulmonary hemosiderosis associated with cow's milk allergy.
      - In addition to hemoptysis, children may have failure to thrive, vomiting, gastrointestinal bleeding, or upper respiratory congestion.
    - Idiopathic pulmonary hemosiderosis (IPH)
      - No evidence of immune-mediated mechanism is found.
      - IPH is diagnosed in most children <7 years or >16 years.
      - Symptoms include respiratory distress, bilateral alveolar infiltrates, and iron deficiency anemia.
- Congenital malformations.
  - Symptoms depend on the nature of the lesion.
  - May be associated with massive hemoptysis or respiratory distress in newborns.
- Primary pulmonary neoplasms.
  - Extremely rare in children, especially immunocompetent children.
  - <5% of tumors reported in the literature have been associated with hemoptysis.

- The most common presentations of primary pulmonary neoplasms in children are
  - — Fever
  - — Cough
  - — Pleural pain

- Other rare causes of hemoptysis without preexisting medical problems.
  - Pulmonary embolism
    - — Pleuritic pain, cough, and dyspnea
    - — Probably associated with oral contraceptive use, recent abortion, or trauma to lower extremities
  - Parasitic lung infections (rare in the United States)
    - — Travel to endemic or sheep-raising areas
    - — Peripheral eosinophilia
  - Arteriovenous malformations
    - — Recurrent epistaxis
    - — Positive family history for hereditary hemorrhagic telangiectasia (Rendu-Osler-Weber syndrome)
      - Cutaneous telangiectasia
  - Catamenial hemoptysis
    - — Occurs with onset of menses
  - Factitious hemoptysis, a form of Munchausen syndrome
    - — A consideration in adolescents with unusual or perplexing symptoms and normal findings
    - — Has been reported in children who had undergone numerous invasive procedures and were biting their oral mucosa to simulate hemoptysis

Preexisting Medical Conditions

- CF.
  - The most common chronic disease associated with hemoptysis.
  - Hemoptysis usually begins in the second or third decade of life and ranges from the production of blood-tinged sputum with excessive coughing to massive bleeding.
  - Massive hemoptysis has an annual incidence of 1% among patients with CF and carries a high mortality rate.
- Bronchiectasis.
  - The number of children with bronchiectasis has decreased because of the decline of tuberculosis and the use of effective vaccines against measles and pertussis.
  - Children with immunodeficiencies, recurrent aspiration, and ciliary dyskinesia may develop bronchiectasis.
  - Most have a history of a chronic productive cough with purulent sputum and changes on the lung examination preceding the onset of hemoptysis.
- Congenital heart disease is becoming a less common cause of hemoptysis because of advances in corrective cardiac surgery.
  - Seen with Eisenmenger complex and pulmonary venous congestion
- Primary or secondary pulmonary hypertension can lead to hemoptysis as a result of thrombo-embolic events.
- Right-ventricular outflow obstruction with increased bronchial arterial circulation.
  - Hemorrhage from enlarged and tortuous bronchial arteries can produce hemoptysis.
- Pulmonary vascular obstructive disease.
  - Hemoptysis occurs because of pulmonary hypertension as well as thrombosis.
  - These vascular changes take years to develop and are usually first observed in adolescents.
- Less common causes in children with a preexisting medical problem include
  - Sickle cell anemia
    - — Acute chest syndrome or pulmonary infarction
  - Aspergillosis in association with CF or asthma
    - — Peripheral eosinophilia and fungi seen on Gram stain of sputum

LABORATORY EVALUATION

- Laboratory tests should depend on findings at history and physical examination.
- Arterial blood gas measurement if the patient has a compromised airway.
  - May aid decisions about need for intensive care
- Urinalysis or specific serologic markers.
  - To determine whether the child has an immunologic disease involving the basement membranes of the kidneys and lungs
- Complete blood cell count with eosinophil count.
  - May help differentiate bacterial from parasitic pneumonia
- Clotting studies.
  - Routinely ordered but invariably normal.
  - Bleeding disorders generally do not cause spontaneous hemoptysis.
- Skin tests.
  - Should always be performed for suspected mycobacteria.

- Other skin tests, or serologic testing for fungi or other infectious agents, should be guided by clinical acumen.

- Pulmonary fluid culture.
  - If sputum is produced or bronchoscopy is performed, it should be cultured and examined for
    - Bacteria
    - Fungi
    - Ova
    - Parasites
    - Mycobacteria
  - Should be stained for the presence of hemosiderin-laden macrophages
- If warranted, early-morning gastric aspirates can be cultured and stained for microorganisms and macrophages.

IMAGING

- The history and physical examination should produce a tentative diagnosis that guides what imaging studies or procedures are needed to reach a definitive diagnosis.
- Chest radiography should be done if the child is stable.
  - Any abnormality on a chest radiograph should be considered as a potential source for the hemoptysis.
  - A normal radiograph does not exclude the thorax as the source of bleeding.
  - In approximately one-third of children with hemoptysis, initial chest radiographic examination reveals no abnormality.
  - Significant findings on chest radiograph include
    - Hilar adenopathy.
    - Air-fluid level in an abscess.
    - Mass.
    - Cavitary lesion.
    - Mediastinal widening.
    - Alveolar infiltrates.
      - A common finding in children with autoimmune diseases that involve the lungs
    - Thickening of the bronchial walls with ring shadows and tramlines suggests bronchiectasis.
  - If a foreign body is suspected, views that may help localize the foreign body include
    - Inspiratory and expiratory radiographs and left and right lateral decubitus radiographs.
      - If a foreign body is causing airway obstruction, the side of the thorax that does not deflate normally on expiration or when dependent is the side with the foreign body.
    - Fluoroscopy.
    - Chest radiograph may be normal if
      - The foreign body is embedded in the mucosa of the airway.
      - Obstruction is partial.
    - The chest radiograph is normal in 25% of children with bronchial foreign bodies and >50% of children with tracheal foreign bodies.
      - Because only 10% of aspirated foreign bodies are radiopaque, a normal chest radiograph does not preclude aspiration.
- Additional imaging studies depend on the presumptive diagnosis.
  - Computed tomography (CT)
    - If the chest radiographic examination is normal or does not add information to that obtained from the history and physical examination, CT can
      - Identify airway abnormalities.
      - Elucidate abnormalities seen on chest radiographs.
      - Define mediastinal structures.
      - Detect parenchymal disease.
      - Help categorize congenital pulmonary malformations and pulmonary vasculitis syndromes.
      - Provide a road map for subsequent bronchoscopy.
    - High-resolution CT has replaced bronchography for diagnosing bronchiectasis.
  - Magnetic resonance imaging (MRI) is appropriate for
    - Evaluating a possible congenital vascular malformation.
    - Differentiation of structures within the mediastinum and hilum.
    - The advantages of MRI do not outweigh its disadvantages, especially if excessive respiratory motion is present or the child's condition is unstable.

DIAGNOSTIC PROCEDURES

- Indications for bronchoscopy include
  - A diagnosis that is in question
  - Massive hemoptysis
  - Incomplete response to therapy
- Timing and need for bronchoscopy, rigid or flexible, depend on
  - Stability of the child's condition
  - Suspected cause of the hemoptysis
- Not every child with hemoptysis needs bronchoscopy.
  - Hemoptysis rarely is the primary indication.
  - If hemoptysis resolves rapidly and completely after medical therapy, bronchoscopy is not needed.
- No studies have compared the use of fiber-optic versus rigid bronchoscopy for evaluating hemoptysis in adults or children.
  - Fiber-optic bronchoscopy may be used for initial evaluation.
  - If an anatomic lesion or foreign body is discovered, rigid bronchoscopy will be needed.
  - Both instruments can be used to
    - Administer therapeutic agents to the airways.
    - Sample bronchial fluids.
    - Take biopsy samples.
  - With the rigid bronchoscope, the bronchoscopist has complete airway control and can
    - Suction through a larger channel.
    - Sample suspicious lesions.
    - Insert packing material to tamponade the bleeding.
    - Remove foreign bodies from the airway (preferred instrument for this purpose).
  - With the fiber-optic bronchoscope
    - General anesthesia is not required.
    - The scope usually is passed transnasally (so that upper airways can also be examined).
    - The scope can be easily maneuvered into the upper lobes and more distal airways.

TREATMENT APPROACH

- The first question to be answered: Is the hemoptysis life-threatening?
  - It is difficult for parents and children to estimate the amount of blood lost.
  - The gravity of the hemoptysis is determined more by the child's clinical status and ability to keep the airway clear than by the amount of blood lost.
  - The greatest danger is not exsanguination but, rather, asphyxiation from aspirated blood.
- Stabilization and evaluation should go on simultaneously in an intensive care setting if the child has evidence of cardiorespiratory distress.
  - Hypotension
  - Orthostatic changes
  - Poor perfusion
  - Pallor
  - Tachypnea
  - Tachycardia
  - Mental status changes
  - Hypoxemia
  - Hypercarbia

SPECIFIC TREATMENT

- CF
  - Mild hemoptysis can be treated with conservative medical therapy, which includes
    - Bed rest
    - Intravenous (IV) or oral antibiotics
    - Withholding of chest physiotherapy
    - Administration of vitamin K
  - Massive or recurrent hemoptysis in CF and other diseases is now treated with bronchial artery embolization.
    - Despite a moderately high rate of recurrent bleeding, embolization can relieve symptoms for a significant period.
- Bronchiectasis
  - Management is similar to that for CF.
- Treatment of acute exacerbations of IPH includes
  - High-dose oral or IV corticosteroids.
  - Supportive care for acute bleeding into the lungs.
  - Controversy exists concerning the need for long-term immunosuppressive therapy.
    - Most physicians caring for children with IPH use azathioprine, chloroquine, or cyclophosphamide to help maintain normal lung function and prevent further episodes of emoptysis.
- Heiner syndrome
  - Although the mechanism whereby milk causes multisystem damage is unclear, elimination of milk from the diet results in dramatic improvement.

WHEN TO REFER

- If evidence for aspiration is definitive, the child should be referred for rigid bronchoscopy to a pediatric surgeon or otolaryngologist experienced in retrieving foreign bodies.
- If the diagnosis is uncertain, the child should be referred to a pediatric pulmonologist or other physician skilled in the use of the fiber-optic/rigid bronchoscope to determine whether a foreign body is present.
- Before bronchial artery embolization, the child should be evaluated by a team consisting of a pulmonologist, thoracic surgeon, and interventional radiologist.

WHEN TO ADMIT

- Evidence of hemodynamic instability
- Mental status changes
- High suspicion of tuberculosis
- Known heart disease
- Chronic lung disease (eg, CF, ciliary dyskinesia, immunodeficiencies)
- High suspicion of pulmonary neoplasm
- Sickle cell anemia, vasoocclusive crisis, or acute chest syndrome
- Inability to protect airway
- Risk for pulmonary embolism
- Lung abscess
- Infants <1 year
- Foreign body aspiration
- Pulmonary hypertension

FOLLOW-UP

- Children with mild hemoptysis who are not hospitalized need close outpatient follow-up.

PROGNOSIS

- Prognosis depends on the underlying cause of hemoptysis.

Henoch-Schönlein Purpura

DEFINITION

- Henoch-Schönlein purpura (HSP) is the most common form of vasculitis in children.
- A small-vessel vasculitis mediated by immunoglobulin A (IgA)-containing immune complexes and characterized by nonthrombocytopenic purpura, abdominal pain, arthralgias, and renal disease.
- Diagnostic criteria published in 1990 by the American College of Rheumatology state that if ≥2 of the following conditions are present, sensitivity and specificity for HSP are >87%:
  - Palpable purpura
  - Initial presentation at ≤20 years
  - Bowel angina
  - Typical biopsy findings

SIGNS AND SYMPTOMS

- Classic presentation.
  - Lower extremity purpura
  - Arthritis
  - Abdominal pain
  - Renal disease
- Mean duration of symptoms is 3–4 weeks.
- Cutaneous manifestations.
  - 50% of patients have a macular-petechial rash.
    - Symmetric
    - Sometimes purpuric
    - Localized predominantly in the extensor surface of the lower extremities, forearms, and buttocks; tends to spare the trunk
  - Lesions tend to fade with time, but new lesions appear for up to 3 months after initial presentation.
  - Nonpitting edema of the scalp, hands, and feet in 30%–70%.
- Joint manifestations in 60%–80% of patients.
  - Knees, ankles, wrists, and fingers are most commonly affected.
  - Joints are usually tender and swollen.
  - Symptoms resolve without residual deformity.
- Gastrointestinal manifestations in 50%–70%.
  - May precede purpura by ≤2 weeks in as many as 20% of children.
  - Higher incidence in patients with renal involvement.
  - Intermittent colicky abdominal pain, vomiting, or gastrointestinal bleeding are most common.
  - ≤5% develop intestinal infarction, perforation, or intussusception.
- Renal inflammation in most patients.
  - Urinary abnormalities in 20%–60%.
  - Responsible for long-term morbidity in affected patients.
  - Renal disease rarely precedes onset of rash, and HSP nephritis usually coincides with or follows cutaneous manifestations.
  - Nephritis usually presents within 4 weeks of onset of joint or gastrointestinal manifestations.
  - Spectrum of renal involvement is broad and may include
    - Microscopic hematuria (transient or persistent)
    - Macroscopic hematuria (initial or recurrent)
    - Proteinuria
    - Nephritic syndrome
    - Nephritic-nephrotic syndrome
  - A small subset of patients may develop progressive renal disease even after having benign urinalysis at presentation.
- Testicular swelling and tenderness in ≤35% of male patients.
  - If present, a thorough evaluation is necessary to rule out testicular torsion.
- Pulmonary hemorrhage and central nervous system involvement have been described.

DIFFERENTIAL DIAGNOSIS

- In a child with acute purpuric and petechial eruptions, clinicians must ensure that the differential diagnosis is kept broad.
- Possible diagnoses include, but are not limited to
  - Acute bacterial infections (invasive meningococcal disease)
  - Rocky Mountain spotted fever
  - Toxic shock
  - Enteroviral infections
  - Endocarditis
  - Idiopathic thrombocytopenic purpura
  - Parvovirus B19
  - Kawasaki disease
  - Acute hepatitis A
- HSP is the most likely diagnosis in a child who presents with
  - Palpable purpura.
  - Abdominal pain.
  - Arthritis/arthralgia.
  - Renal involvement.
  - Other diagnoses should be considered in a child who presents without the characteristic purpuric rash.

DIAGNOSTIC APPROACH

- Diagnosis of HSP is based on clinical findings.

LABORATORY FINDINGS

- No laboratory tests specific for HSP.
- Measurement of serum IgA levels is not helpful in confirming diagnosis or providing prognostic information.
- To screen for renal involvement
  - Urinalysis should be performed at diagnosis and at least monthly for 6 months even if prior test result was negative.
  - Blood pressure should be checked at diagnosis and subsequent visits for at least 6 months, even if previously within reference range.
- In patients with HSP and abnormal urinary sediment or elevated blood pressure, test for kidney function.
- In atypical presentations of HSP, consider evaluating other possible causes for clinical findings with
  - Complete blood cell count
  - Coagulation studies
  - Complement levels

DIAGNOSTIC PROCEDURES

- Renal biopsy is not indicated in all patients with a diagnosis of HSP.
  - It should be considered in patients with
    - Significant proteinuria for ≥1 months
    - Renal insufficiency
    - Hypertension
    - Nephrotic syndrome

TREATMENT APPROACH

- Once the diagnosis of HSP is established, supportive care is the most important first step.
- Careful attention to the following items will be the cornerstone of treatment for most patients:
  - Nutrition
  - Volume status
  - Vital signs (especially blood pressure)
  - Urinalysis
- Specific therapy for HSP remains controversial.
- Mild cases of HSP do not require treatment, provided they are closely monitored, especially during the first 6 months.
- Significant abdominal pain may require steroids.
  - High initial doses followed by slow taper
- Children who do not show any urinary abnormalities within 6 months of diagnosis rarely develop chronic kidney disease (CKD).
  - Therefore, steroids or other immunosuppressants are not indicated for prevention.
- Children who show only isolated hematuria or proteinuria have a very low risk of CKD (1.6%).
  - This group should receive supportive care only and not more aggressive treatment.
- Patients who have nephritic or nephrotic syndrome have a much higher risk of CKD (10%–19.5%).
  - This group merits serious consideration for aggressive therapy.
  - Girls are especially at risk of CKD (2.5× higher than their male counterparts) and will likely benefit more from therapy.

SPECIFIC TREATMENTS

Steroids

- Long-term follow-up of 219 patients (83 children <16 years and 136 adults) with biopsy-proven HSP found
  - 60% of children and 72% of adults had been treated with steroids.
  - 14% of children and 22% of adults had received immunosuppressants.
  - Use of steroids or immunosuppressants failed to show any advantage over supportive care.
  - 7% of these children ended up receiving dialysis after a mean follow-up of 6.7 years.
  - Girls were at higher risk of eventual dialysis.
- Another study of 27 children with HSP nephritis treated with long-term immunosuppression over 10 years found
  - Those with high-grade HSP nephritis had persistent renal abnormalities on long-term follow-up.
- Use of steroids in patients with HSP should be decided on individual bases; cases considered for steroid treatment should be referred to nephrologists.
- Steroids for extrarenal manifestations may be helpful.
  - Randomized, double-blind, placebo-controlled trial of early steroid therapy that followed patients for 6 months.
  - Of the 171 patients who were included, 84 were treated with prednisone and 87 received placebo.
  - Endpoints were renal involvement at 1, 3, and 6 months and healing of extrarenal symptoms.

- Use of prednisone (1 mg/kg/d for 2 weeks, with weaning over the subsequent 2 weeks) was effective in reducing the intensity of abdominal pain and joint pain (4.6 vs 7.3; $P = 0.030$).
- Prednisone did not prevent development of renal symptoms, but it was effective in treating them.
- Renal symptoms resolved in 61% of prednisone recipients and 34% of placebo recipients.
- Conclusion: General use of prednisone in HSP is not supported, but patients with disturbing symptoms may benefit from early treatment.
  - Prednisone reduces extrarenal symptoms and is effective in altering, but not preventing, the course of renal involvement.
- A long-term follow-up study found that patients with nephritis at onset of disease had increased risk for hypertension or urinary abnormalities 8 years later.
  - No differences between placebo and prednisone groups, leading to conclusion that early prednisone therapy does not affect long-term outcome and should not be routine.

Fish Oil, Enalapril, and Angiotensin-converting Enzyme (ACE) Inhibitors

- Fish oil and enalapril for hypertension, hematuria, and proteinuria.
  - Children in a study were given 1,000 mg fish oil twice daily and enalapril 2.5–10 mg/d.
  - Enalapril was subsequently stopped in all patients within 1 year.
  - 6-month follow-up off ACE inhibition but on fish oil.
    - Renal function remained the same (mean creatinine level, 0.6 mg/dL) before and after treatment.
    - Hypertension (135/82 vs 100/54; $P < 0.05$) remained better controlled.
    - Proteinuria (1,041 mg/d vs 104 mg/d; $P < 0.05$) remained minimal.
  - Conclusion: This case series was very small, but fish oil is a benign treatment that may provide other added benefits, such as reduction of hypertriglyceridemia.
  - Fish oils (omega-3 acid ethyl esters) have been shown to be promising in IgA nephropathy, which many researchers think is part of the spectrum of disease related to HSP.
  - Anti-inflammatory and immune-modulating effects of fish oil have been demonstrated in other studies.
- ACE inhibitors are also indicated for control of hypertension, especially for patients with proteinuria.
- Cyclosporine and prednisone, plasmapheresis, tonsillectomy, dapsone, and cyclophosphamide have been tried, with varying degrees of success.
  - These approaches have the possibility of toxicity and many lack verification.

WHEN TO ADMIT

- Toxic appearance (febrile, lethargic, hypotensive, or hypertensive, with altered mental status or "not acting themselves").
- Abdominal pain may indicate acute appendicitis, intussusception, small-bowel obstruction or infarction, or pain caused by HSP.
  - Obtaining a surgical consultation is advisable if abdominal pain is particularly severe or out of proportion to findings on physical examination.
- A significant reduction in urine output for age and weight or inability to keep fluids down.
- Significant gastrointestinal bleeding.
- Significant (>25%) alteration from reference range in the patient's kidney function (serum creatinine).

WHEN TO REFER

- Patients should be monitored by their pediatrician and referred to a pediatric nephrologist if they have
  - Proteinuria or hematuria
  - Hypertension
- Significant and persistent signs of kidney inflammation (nephritic or nephrotic syndrome)
- Acute kidney injury (elevation in blood, urea, nitrogen, or creatinine levels)

FOLLOW-UP

- Patients must be monitored for changes in renal function and for hypertension.

COMPLICATIONS

- 2%–5% of patients with renal involvement progress to end-stage renal disease.

PROGNOSIS

- Up to one-third of children have at least one recurrence.
- HSP nephritis.
  - When mild, tends to resolve without any particular intervention
- Predictors of poor renal prognosis.
  - Abnormal creatinine clearance at 3 years after onset
  - Ultrastructural abnormalities in the renal biopsy

DEFINITION

- *Hepatitis* describes inflammation of the liver and does not imply a cause.
  - Hepatitis in children may be caused by infectious, autoimmune, and metabolic conditions, or drug toxicity.
- *Fulminant hepatic failure* is hepatic encephalopathy within 8 weeks of onset of illness.
  - Definition is problematic in children because
    - It is difficult to detect encephalopathy in infants and young children.
    - Encephalopathy may present late or not at all.
  - Important components of definition are lack of preexisting liver disease and severe impairment of hepatic function evidenced by prothrombin time >4 seconds over control values and an international normalized ratio (INR) >1.5 that is unresponsive to large doses of vitamin K.

SIGNS AND SYMPTOMS

- Common presentations include
  - Jaundice
  - Incidental finding of elevated liver enzymes during routine workup
  - Fulminant hepatic failure
- Clinical syndromes of viral hepatitis vary from asymptomatic to fulminant hepatic failure, depending on the virus and host factors.
  - Acute viral hepatitis may also progress to chronic liver disease, particularly with hepatitis B virus (HBV) and hepatitis C virus (HCV).
  - Clinical features of acute viral hepatitis are shown in **Table 1.**
- Initial symptoms of hepatitis A virus (HAV) may be nonspecific and include
  - Fever.
  - Malaise.
  - Anorexia.
  - Nausea.
  - Vomiting.
  - Upper abdominal discomfort.
  - Darkening of the urine and enlargement and tenderness of the liver.
  - Jaundice (infrequent in young children).
  - Disease is rarely fulminant.
    - A small percentage of patients with HAV may have a relapsing or protracted course.
  - Children with acute HAV may be completely asymptomatic but are still infectious and, therefore, serve as a silent reservoir of disease.
- HBV.
  - HBV acquired perinatally or horizontally at a very young age is generally asymptomatic.
  - Onset is usually insidious.
  - Extrahepatic manifestations, such as skin rash and arthralgia, are common and may be prodromal.
  - Duration of illness is usually 4–6 weeks.
  - Liver cirrhosis is encountered in 3%–5% of children with chronic HBV.
- Acute HCV infection is asymptomatic in most children.
  - Acute liver failure and cirrhosis have been reported in infancy.
  - 2 characteristic clinical features of HCV infection are
    - Fluctuation in the serum aminotransferase concentrations
    - Progression to chronicity in 50%–90% of patients
  - Most patients remain asymptomatic without stigmata of chronic liver disease.
  - Liver histologic test shows mild to moderate hepatitis and fibrosis increases with duration of infection but in an unpredictable manner.
- Acute hepatitis D virus (HDV) infection in a child who is a chronic HBV carrier may produce a severe episode of hepatitis with fulminant hepatic failure or chronic hepatitis.
- Hepatitis E virus (HEV) is similar clinically to HAV.
  - Cholestasis may be more common than with HAV, and elevation of serum aminotransferases is modest.
  - Its most unusual clinical feature is a high mortality rate in pregnant women (~10%).
- The mode of presentation of autoimmune hepatitis (AIH) is highly variable.
  - Hepatomegaly, splenomegaly, and jaundice are common.
  - Autoimmune hepatitis is strongly associated with inflammatory bowel disease and may precede or follow colitis.
  - Associated extrahepatic manifestations include
    - Nephrotic syndrome
    - Autoimmune thyroiditis
    - Behçet syndrome
    - Crohn disease
    - Insulin-dependent diabetes
    - Urticaria pigmentosa
    - Vitiligo
    - Hypoparathyroidism
    - Addison disease

Table 1. Clinical Features of Acute Viral Hepatitis

	HAV	HBV	HCV
Characteristics			
Age distribution	Children and young adults	All age groups	All age groups
Route of infection	Predominantly fecal-oral	Parenteral	Parenteral
Incubation period (d)	15–40	50–180	20–90
Onset	Acute	Insidious	Insidious
Duration of clinical illness	Weeks	Weeks to months	Weeks to months
Virus Presence			
Feces	Late incubation, acute	May be present	Absent
Blood	Late incubation, acute	Late incubation, acute, may persist for months	Present chronically
Signs and Symptoms			
Fever	High, common early	Moderate, less common	Moderate, less common
Nausea and vomiting	Common	Less common	Less common
Anorexia	Severe	Mild to moderate	Mild to moderate
Arthralgia or arthritis	Rare	Common	Absent
Rash or urticaria	Rare	Common	Absent
Laboratory Findings			
Aminotransferase elevation	1–3 wk	Months	Fluctuates for months
Bilirubin elevation	Weeks	May be months	Unusual
HBsAg	Absent	Present	Absent
Severity	Unusually mild	Often severe	Unusually mild
Progression to chronic hepatitis	Rare	More common	High rate
Immunity	Homologous, lifelong	Homologous, lifelong	Unusual
Prevention	Immune serum globulin, vaccine	Hyperimmune globulin; vaccine	Screen donor blood

Abbreviations: HAV, hepatitis A virus; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus.

Modified from Gershon AA, Hotez PJ, Katz SL. *Krugman's Infectious Diseases of Children.* 11th ed. St Louis, MO: Mosby; 2004; and deBelle RC, Lester R. Current concepts of acute and chronic viral hepatitis. *Pediatr Clin North Am.* 1975;22(4):943–961. Copyright © Elsevier, with permission.

- Fibrosis may be seen to a variable degree.
- True cirrhosis may be present.

- Metabolic diseases.
  - Nonalcoholic steatohepatitis (NASH) is seen in children with a significant number of risk factors, including
    - Obesity (body mass index >30 kg/m^2)
      - Many children are obese, but only a few have NASH.
    - Diabetes
    - Insulin resistance
    - Hypertriglyceridemia
  - Hereditary fructose intolerance (HFI) in the older child with an aversion to fructose-containing products who, after inadvertent ingestion, develops
    - Vomiting
    - Elevation of serum aminotransferases
- To evaluate for drug- or toxin-induced hepatitis, a complete medical history should be obtained for
  - Prescribed medications
  - Herbal teas
  - Poisons
  - Wild mushrooms

DIFFERENTIAL DIAGNOSIS

Infectious

- Hepatitis A, B, C, D, E, G
- Adenovirus
- Epstein-Barr virus
- Cytomegalovirus
- Varicella zoster
- Human herpesvirus 6
- Parvovirus B19
- Echovirus
- Coxsackievirus
- Rubeola virus

Autoimmune

- Type 1
- Type 2
- Sclerosing cholangitis (neonatal and child forms)

Metabolic

- α_1-Antitrypsin deficiency
- Galactosemia
- Hereditary tyrosinemia
- HFI
- Progressive familial intrahepatic cholestasis types 1, 2, and 3
- Paroxysmal diseases
- Mitochondrial hepatopathies
- Neonatal hemochromatosis
- Glycogen storage disease
- Niemann-Pick disease type C
- Inborn errors of bile acid metabolism
- Wilson disease
- NASH

Drug-Induced

- Sodium valproate
- Halothane
- Phenytoin
- Herbal medications
- Recreational drugs (eg, Ecstasy)
- Toxins (eg, *Amanita phalloides* [wild mushrooms])

Other

- Alagille syndrome
- Cystic fibrosis
- Ischemia
- Trauma (including child abuse)

Elevated Liver Enzymes Without Hepatitis

- Myopathies
- Bone disorder
- Transient hyperphosphatasia
- Celiac disease

Fulminant Hepatic Failure

- Acetaminophen toxicity is the most common cause of fulminant hepatic failure in the United States.
- In infancy, metabolic disorders may cause fulminant failure.
  - Galactosemia
  - HFI
  - Tyrosinemia
  - Gestational alloimmune liver disease (formerly called neonatal hemochromatosis)
- In children beyond infancy, the following causes should be considered in the etiology of fulminant hepatic failure:
  - Wilson disease
  - AIH, particularly type 2
  - Medications
  - Toxins

Newborns and Infants

- Other conditions that should be considered in a newborn or an infant with jaundice include
  - α_1-AT deficiency
  - Cystic fibrosis
  - Defects in amino acid synthesis
  - Organic acid synthesis and fatty acid oxidation
  - Glycogen storage disease
  - Niemann-Pick type C disease

- The association of renal Fanconi syndrome and clotting abnormalities that are unresponsive to vitamin K therapy suggests tyrosinemia.
- Gestational alloimmune liver disease (formerly called neonatal hemochromatosis) may also present with hepatitis but often occurs with acute liver failure.
- Alagille syndrome.
  - Diagnosis in the proband still relies largely on the initial clinical criteria and is based on the association of bile duct paucity together with at least 3 of
    - Typical facies
    - Posterior embryotoxon (ophthalmologic examination)
    - Butterfly vertebrae (seen on chest radiograph)
    - Consistent cardiac disease (eg, pulmonary stenosis)
    - Renal disease
  - Other features include
    - Markedly elevated gamma-glutamyl transferase (GGT)
    - Hypercholesterolemia
    - Growth retardation
    - Intracranial bleeding
  - Genetic testing available in selected centers may be useful in family studies, as the penetrance is variable.
- Tyrosinemia.
  - The usual presentation in infants is acute liver failure with pronounced coagulopathy.
- Galactosemia exhibits in the neonatal period with
  - Cholestatic jaundice
  - Hypoglycemia
  - Encephalopathy
  - Vomiting
  - Failure to thrive
  - Hepatitis
- HFI manifests as
  - Metabolic acidosis
  - Hypoglycemia
  - Liver failure

Children

- Viral hepatitis, particularly HAV, HBV, HCV, and Epstein-Barr virus, should be actively sought in this age group.
- HBV should be considered in the differential diagnosis of serum sickness-like illness.
- Wilson disease should be considered in assessment of pediatric liver disease, because of its variable presentation and availability of effective therapy.
- AIH
  - Type 1 is characterized by the presence of antinuclear antibody (ANA) and anti–smooth-muscle antibody.
  - Type 2 is characterized by the presence of anti-liver-kidney microsomal antibodies (LKM).
- NASH
  - Fat in the liver is associated with inflammation.
  - Consider in prepubertal children with obesity.

DIAGNOSTIC APPROACH

- Careful clinical history and examination are important in making a timely diagnosis and avoiding unnecessary investigations.

LABORATORY FINDINGS

Jaundice in Newborns and Infants

- Investigations in the newborn or infant in whom a cause of hepatitis is not obvious should include serology for viruses and general investigations, such as
  - Blood ammonia.
  - Serum glucose.
  - Blood gases with pH.
  - Blood lactate.
  - Urine metabolic screen and reducing substances.
  - Red blood cell galactose-1-phosphate uridyl transferase.
  - Thyroid function tests.
  - Serum and urine bile acids.
  - More sophisticated tests are required for many metabolic and inherited disorders.

Child With Jaundice

HAV

- HAV RNA can be detected in serum and stool as early as 2–3 weeks before acute illness.
- HAV RNA can be detected in serum and stool up to 1 week after the onset of illness.
- Recovery in the stool decreases as jaundice becomes evident.
- HAV immunoglobulin G (IgG) antibody is present at least 10 years after infection.

HBV

- Its double-stranded overlapping DNA codes for
  - Hepatitis B surface antigen (HBsAg)
  - Hepatitis B core antigen (HBcAg)
  - Hepatitis B e antigen (HBeAg)
  - DNA polymerase
- HBsAg has been found in all body secretions and excretions from infected persons.

- Presence of HBsAg in the serum implies HBV infection.
- First marker to appear; detected 2 weeks–6 months after exposure
- Children with HBV infection are initially HBsAg and HBeAg positive.
- HBeAg reflects active viral replication and infectivity.
- During this immunotolerant stage, which may persist for years, viral replication and serum HBV DNA levels are very high.
  - Serum aminotransferase levels fluctuate and may be in the upper limit of normal range.
  - HBV aminotransferase elevation usually peaks ~1 month after the onset of illness.
- During childhood, conversion from HBeAg to anti-HBeAg may occur spontaneously, at a rate of 3% per year, although rates vary with the mode of acquisition.
- Seroconversion to anti-HBeAg is often preceded by a transient elevation in serum aminotransferases.
- After anti-HBeAg seroconversion, HBV DNA levels remain low or undetectable.
  - In this state, children may once again develop fluctuations of alanine aminotransferase and a rise in DNA levels, indicating increased replication of a pre-core mutant virus that does not produce e antigen.
- Most children remain HBsAg positive, and this chronic carrier state is not generally associated with overt disease.
- Annual HBsAg clearance rate is low (1%–2%) and may be associated with persistence of HBV DNA.
- HBV DNA is detectable in serum very early in the infection, but its measurement is limited by the sensitivity of the techniques used.
- HBV DNA is now reported in international units per milliliter (IU/mL).
- Anti-hepatitis B surface antibody indicates immune response to immunization or past infection.
- Presence of anti-hepatitis B core antibody (HBc), which appears 3–5 weeks after HBsAg, implies exposure to the native virus.
- Anti-HBc does not appear after vaccination.

HCV

- Presence of antibodies to HCV implies exposure to HCV but does not confer protective immunity.
  - Most laboratories currently use third-generation enzyme-linked immunosorbent assay with >99% sensitivity and specificity.
  - These test results become positive weeks after exposure to the virus.
- Highly sensitive polymerase chain reaction (PCR) assay result becomes positive within days after exposure to the virus.
  - Assays for viral detection may be quantitative or qualitative.
  - Quantitation is an important component of guiding therapy.
  - Quantitative assays are used more often.
  - As with HBV infection, an IU has been adopted to overcome variability between laboratories and commercially available assays.
- Vertically acquired infection is confirmed by
  - Persistence of anti-HCV antibody >18 months.
  - Presence of HCV RNA in serum after the first 3 months of life.
  - PCR testing before this period is unreliable.

HDV

- A test for anti-HDV is commercially available.

HEV

- Cholestasis may be more common than with HAV.
- Elevation of serum aminotransferase levels is modest.
- Serologic identification of anti-HEV IgM is diagnostic, and real-time PCR has recently been developed.

Hepatitis G Virus (HGV) and Torque Teno Virus (TTv)

- Diagnosed by detection of HGV RNA and TTv DNA by PCR methods

AIH

- Diagnosis relies on a combination of hypergammaglobulinemia and increased ANA, smooth-muscle antibody, or LKM antibody titers.
- In 1999, the International Autoimmune Hepatitis Group modified a scoring system to diagnose AIH in adults.
  - Useful in children, particularly when a ratio of GGT to aspartate aminotransferase (AST) was used instead of the ratio of alkaline phosphatase to AST.
  - The GGT to AST ratio is better at detecting autoimmune disease with a biliary component, such as overlap syndrome.
- Histologically, portal tracts are infiltrated by lymphocytes and plasma cells.
- Inflammatory cells often infiltrate the parenchyma, accompanied by necrosis of cells at the periphery of the hepatic lobule (piecemeal necrosis).

Metabolic Diseases

- No single test is available to diagnose Wilson disease.
  - The combination of ≥2 of the following findings is highly suggestive:
    - Decreased serum ceruloplasmin level (<20 mg/dL)
    - Elevated urinary copper excretion (>100 mcg/24 hours)
    - Elevated liver copper concentration (>250 mcg/g of dry weight)
    - Kayser-Fleischer rings
  - Genetic confirmation is available in some centers.

Drug- or Toxin-Induced Hepatitis

- Serum acetaminophen should be measured on presentation and appropriate therapy instituted immediately.
- Urine toxicology screen should be performed when the index of suspicion is high.

Abnormal Liver Enzyme Levels

- Systemic disorders may produce raised aminotransferase levels.
- Elevated levels of aminotransferases have been found in 32% of children with celiac disease.
  - Celiac screening should be performed on all children with unexplained elevation of serum aminotransferase levels after hepatologic causes have been excluded.
  - Evidence of muscle disorders (serum creatine kinase) and red cell disorders (complete blood cell count and peripheral smear, reticulocyte count, and haptoglobin levels) should be performed if there is no clinical evidence of liver disease.

Progressive Familial Intrahepatic Cholestasis (PFIC)

- PFIC 1, 2, 3: serum bile acids raised
- PFIC 1, 2: GGT low
- PFIC 3: GGT high

IMAGING

- Ultrasonography
  - In NASH, fatty liver can be identified on sonography by uniform or patchy increased echogenicity.

DIAGNOSTIC PROCEDURES

- Liver biopsy
  - When chronic liver disease is suspected and cannot be diagnosed.
  - To determine the degree of inflammation and fibrosis, which may influence treatment.
  - Needle biopsy is usually adequate.
  - Risks are low when clotting function is normal, ultrasonographic guidance is used, and the biopsy is performed by an experienced physician.
  - Biopsy sample should be sent for histologic testing with additional stains (eg, copper, iron) if necessary.
  - If a metabolic liver disease is suspected, a small sample should be preserved in glutaraldehyde for electron microscopy.
  - If Wilson disease is suspected, hepatic copper should be quantified.
    - Obtaining a second biopsy core is usually necessary for this purpose.

SPECIFIC TREATMENTS

HAV

- Vaccines.
  - 2 inactivated vaccines against HAV are licensed in the United States for children aged 1–18 years and adults.
  - Vaccine is given in a 2- or 3-dose schedule depending on the formulation (**Table 2**).
  - The vaccine is now recommended for all children 1–18 years of age.
  - Indications for HAV vaccination.[1]
    - All children in the United States 12–23 months of age
    - Catch-up immunization of unimmunized children 2–18 years of age
      - Especially with increase in incidence or ongoing outbreaks among children and adolescents
    - Travelers to endemic areas
    - Close contacts of newly arrived international adoptees
    - Patients with chronic liver disease
    - Patients with clotting factor disorders
    - Men who have sex with men
    - Users of injection and illicit drugs
    - Patients at high risk of exposure secondary to occupation

Table 2. Recommended Doses and Schedules for Inactivated Hepatitis A Vaccines[a]

Age	Vaccine	Hepatitis A Antigen Dose	Volume per Dose (mL)	Number of Doses	Schedule
12 mo–18 y	Havrix	720 ELU	0.5	2	Initial and 6–12 mo later
12 mo–18 y	Vaqta	25 U[b]	0.5	2	Initial and 6–18 mo later
19 y or older	Havrix	1,440 ELU	1.0	2	Initial and 6–12 mo later
19 y or older	Vaqta	50 U[b]	1.0	2	Initial and 6–18 mo later
18 y or older	Twinrix[c]	720 ELU	1.0	3 or 4	Initial, 1 mo, and 6 mo later OR Initial, 7 days, and 21–30 days, followed by a dose at 12 mo

Abbreviation: ELU, enzyme-linked immunosorbent assay units.

[a] Havrix and Twinrix are manufactured by GlaxoSmithKline Biologicals (Research Triangle Park, NC); Vaqta is manufactured and distributed by Merck & Co, Inc. (Kenilworth, NJ).

[b] Antigen units (each unit is equivalent to approximately 1 mcg of viral protein).

[c] A combination of hepatitis B (Engerix-B, 20 mcg) and hepatitis A (Havrix, 720 ELU) vaccine (Twinrix) is licensed for use in people 18 years and older in a 3- or 4-dose schedule.

From American Academy of Pediatrics. Hepatitis A. In: Kimberlin DW, Brady MT, Jackson MA, Long SS, eds. *Red Book: 2015 Report of the Committee on Infectious Diseases.* 30th ed. Elk Grove Village, IL: American Academy of Pediatrics; 2015:391–399.

- No particular diet or restriction of activity appears to affect course or outcome of acute viral hepatitis because recovery of HAV in the patient's stool decreases rapidly after the onset of jaundice.
- Return to school at this point, provided that the child feels well, does not seem to present an undue risk of infection to others.
- Household contacts are already likely to be infected by the time of diagnosis.
  - Infection-control measures should be instituted, including
    - Scrupulous hand washing
    - Use of disposable eating utensils until jaundice clears
- Pooled serum Ig given within 2 weeks postexposure is effective in preventing symptomatic infection, as is immunization within an 8-day window.
- Ig should be given to household contacts, institutional contacts, and persons exposed in common source outbreaks.
- Immunoprophylaxis should be given to household, sexual, child care center, and hospital contacts and may be recommended in some situations for schoolroom contacts and persons exposed in common source outbreaks.
- Newborns born of infected mothers do not need special care if the mother is not jaundiced.
- Children traveling to endemic areas should be immunized prophylactically.
  - Vaccination is preferable.
    - If travel is imminent (in <1 month), IgG may be substituted.

HBV

- History of vaccination in the United States.
  - In 1991, universal newborn HBV immunization.
  - In 1995, routine vaccination of all children aged 11–12 years.
  - In 1999, inclusion of children and adolescents <18 years who had not been vaccinated previously.
  - These efforts resulted in a significant reduction of HBV in children.
  - The rate of acute HBV infection in children and adolescents decreased by 89% during 1990–2002.
- Racial disparities in hepatitis B incidence have narrowed.
- A recent study showed that most homeless inner-city adolescents aged 13–18 years have not been vaccinated against hepatitis B.

- Persons who should receive HBV immunization include[2]
  - All neonates (Neonates of HBsAg-positive mothers require postexposure immunoprophylaxis with hepatitis B immune globulin [HBIG] and vaccine.)
  - All children and adults not vaccinated as neonates
  - Inmates of juvenile detention correctional facilities
  - People at risk of infection by sexual exposure
    - Sex partners of HBsAg-positive people
    - Sexually active people who are not in a long-term mutually monogamous relationship (eg, people with >1 sex partner during the previous 6 months)
    - People seeking evaluation or treatment for a sexually transmitted infection
    - Men who have sex with men
  - People at risk of infection by percutaneous or mucosal exposure to blood
    - Current or recent injection drug users
    - Household contacts of HBsAg-positive people
    - Residents and staff of facilities for people with developmental disabilities
    - Health care and public safety workers with reasonably anticipated risk of exposure to blood or blood-contaminated body fluids
    - People with end-stage renal disease, including pre-dialysis, hemodialysis, peritoneal dialysis, and home dialysis
    - People with diabetes mellitus who are >19 years
  - Others
    - International travelers to regions with high or intermediate levels (HBsAg prevalence ≥2%) of endemic HBV infection
    - People with chronic liver disease
    - People with HIV infection
    - All other people seeking protection from HBV infection
- Detailed recommendations on doses and post-exposure prophylaxis are provided in **Tables 3** and **4.**
- Recommendations for HBV prophylaxis after exposure to blood or body fluids are provided in **Table 5.**
- A baby born to an HBsAg-positive mother or a mother who has had hepatitis B during pregnancy should be given
  - 0.5 mL of HBIG intramuscularly (IM) within the first 12 hours of life *and*
  - 0.5 mL of HBV vaccine IM before hospital discharge but definitely within the first week of life *and*
  - 0.5 mL of HBV vaccine IM at 1 and 6 months
- Data linking breastfeeding to the acquisition of viremia are equivocal.
  - HBsAg-positive mothers whose infants have received immunoprophylaxis may breastfeed without risk of transmitting HBV.
- HBV immunization also protects against HDV infection.
- The decision to treat a child with HBV is complex and should be made in conjunction with a pediatric hepatologist.
- 2 major classes of medication are available.
  - Interferons
  - Nucleoside/tide analogs
- Treatment does not usually eradicate the virus.
- Treatment can result in seroconversion, suppression of the viral load, and a reduction in inflammation.
- Treatment is generally offered to children who
  - Have prolonged significantly abnormal liver function tests and do not seroconvert spontaneously
  - Have evidence of hepatocellular injury on biopsy
- Regardless of treatment, all children with HBV should be monitored for signs of evolving chronic liver disease.
  - Clinical examination
  - Liver function tests
  - α-Fetoprotein
  - Viral markers

HCV

- No vaccine is available for prevention of HCV.
- Natural infection does not protect from reinfection with the same or different genotypes.
- The most important strategies for controlling hepatitis C include
  - Screening donor blood for anti-HCV
  - Identifying and educating persons at risk
  - Establishing risk-minimization programs for intravenous (IV) drug users
- Screening should include
  - Injection drug users
  - Patients receiving hemodialysis
  - Recipients of ≥1 units of blood or blood products before 1992
  - Children with clinical non-A, non-B hepatitis
  - Children >18 months born to mothers infected with HCV
  - International adoptees born to high-risk mothers

Table 3. Guide to Postexposure Immunoprophylaxis of Unimmunized People to Prevent Hepatitis B Virus Infection

Type of Exposure	Immunoprophylaxis[a]
Household contact of HBsAg-positive person	Administer hepatitis B vaccine series.
Discrete exposure to an HBsAg-positive source[b]	
• Percutaneous (eg, bite, needlestick, non-intact skin) or mucosal exposure to HBsAg-positive blood or body fluids	Administer hepatitis B vaccine + HBIG; complete vaccine series.
• Sexual contact or needle sharing with an HBsAg-positive person	Administer hepatitis B vaccine + HBIG; complete vaccine series.
• Victim of sexual assault/abuse by a perpetrator who is HBsAg-positive	Administer hepatitis B vaccine + HBIG; complete vaccine series.
Discrete exposure to a source of unknown HBsAg status	
• Percutaneous (eg, bite, needlestick) or mucosal exposure to blood or body fluids with unknown HBsAg status	Administer hepatitis B vaccine series.
• Victim of sexual assault/abuse by a perpetrator with unknown HBsAg status	Administer hepatitis B vaccine series.
• Susceptible child biting someone with chronic HBV infection	Initiate or complete the hepatitis B vaccine series. Do not give HBIG (assumes no oral mucosal disease when the amount of blood transferred from a child with chronic HBV infection is small).

Abbreviations: HBIG, hepatitis B immune globulin; HBsAg, hepatitis B surface antigen.

[a] Immunoprophylaxis should be administered as soon as possible, preferably within 24 hours after exposure. Studies are limited on the maximum interval after exposure during which postexposure prophylaxis is effective, but the interval is unlikely to exceed 7 days for percutaneous exposures and 14 days for sexual exposures.

[b] If person previously was immunized with hepatitis B vaccine series, administer hepatitis B vaccine booster dose.

From American Academy of Pediatrics. Hepatitis B. In: Kimberlin DW, Brady MT, Jackson MA, Long SS, eds. *Red Book: 2015 Report of the Committee on Infectious Diseases*. 30th ed. Elk Grove Village, IL: American Academy of Pediatrics; 2015:400–423.

- Patients with HCV infection should
  - Avoid hepatotoxic medications and alcohol.
  - Receive vaccination against HAV and HBV infections to prevent additional liver damage.
- Treatment regimens for HCV have advanced considerably with the development of individualized treatment algorithms based on genotype of the virus and response rates at various times during therapy.
- The development of a genetic marker for interferon sensitivity (IL28B) 76, as well as a marker for the risk of hemolysis with ribavirin 77, have allowed a further refining of individualized treatment pathways.
- Most of this work has not yet been validated in children, but studies are underway.
- Treatment of HCV (unlike HBV) can eradicate the virus and, hence, is a much more attractive proposition.
- Powerful viral suppressing polymerase inhibitors, when used in interferon-free regimens, produce viral clearance in those with difficult-to-treat genotypes and those in whom previous therapy failed.
- The decision to treat is based on many factors; treatment requires close monitoring and, hence, should only be undertaken by those experienced in treating.

Table 4. Recommended Doses of Hepatitis B Vaccines

	Vaccine[a]		Combination Vaccines		
Patients	Recombivax HB[b] dose, µG (mL)	Engerix-B[c] dose, µG (mL)	Comvax[d] dose, µG (mL)	Pediarix[e] dose, µG (mL)	Twinrix[f] dose, µG (mL)
Infants of HBsAg-negative mothers and children and adolescents <20 y	5 (0.5)	10 (0.5)	5 µG HBsAg (0.5)	10 µG HBsAg (0.5)	NA
Infants of HBsAg-positive mothers (HBIG [0.5 mL] also is recommended)	5 (0.5)	10 (0.5)	5 µG HBsAg (0.5)	10 µG HBsAg (0.5)	NA
Adolescents 11–15 y of age[b]	10 (1)	NA	NA	NA	NA
Adults ≥20 y	10 (1)	20 (1)	NA	NA	20 (1)
Adults undergoing dialysis and other immunosuppressed adults	40 (1)[g]	40 (2)[h]	NA	NA	NA

Abbreviations: HBIG, hepatitis B immune globulin; HBsAg, hepatitis B surface antigen; NA, not applicable.

[a] Both vaccines are administered in a 3-dose schedule at 0, 1, and 6 months; 4 doses may be administered if a birth dose is given and a combination vaccine is used (at 2, 4, and 6 months) to complete the series. Only single-antigen hepatitis B vaccine can be used for the birth dose. Single-antigen or combination vaccine containing hepatitis B vaccine may be used to complete the series.

[b] Available from Merck & Co Inc. (Kenilworth, NJ). A 2-dose schedule, administered at 0 months and then 4 to 6 months later, is licensed for adolescents 11 through 15 years of age using the adult formulation of Recombivax HB (10 mcg [Merck & Co Inc]).

[c] Available from GlaxoSmithKline Biologicals (Research Triangle Park, NC). The US Food and Drug Administration also has licensed this vaccine for use in an optional 4-dose schedule at 0, 1, 2, and 12 months for all age groups. A 0-, 12-, and 24-months schedule is licensed for children 5 through 16 years of age for whom an extended administration schedule is appropriate based on risk of exposure.

[d] Available from Merck & Co Inc. A combination of hepatitis B (Recombivax, 5 mcg) and *Haemophilus influenzae* type b (PRP-OMP) vaccine is approved for use at 2, 4, and 12 through 15 months of age (Comvax). This vaccine should not be administered at birth, before 6 weeks of age, or after 71 months of age.

[e] A combination of diphtheria and tetanus toxoids and acellular pertussis (DTaP), inactivated poliovirus (IPV), and hepatitis B (Engerix-B 10 mcg) is approved for use at 2, 4, and 6 months of age (Pediarix [GlaxoSmithKline]). This vaccine should not be administered at birth, before 6 weeks of age, or at 7 years or older.

[f] A combination of hepatitis B (Engerix-B, 20 mcg) and hepatitis A (Havrix, 720 enzyme-linked immunosorbent assay units [ELU]) vaccine; Twinrix is licensed for use in people 18 years and older in a 3-dose schedule at 0, 1, and 6 months. Alternately, a 4-dose schedule at days 0, 7, and 21 to 30 followed by a booster dose at 12 months may be used.

[g] Special formulation for adult dialysis patients given at 0, 1, and 6 months.

[h] Two 1-mL doses given in 1 or 2 injections in a 4-dose schedule at 0, 1, 2, and 6 months of age.

From American Academy of Pediatrics. Hepatitis B. In: Kimberlin DW, Brady MT, Jackson MA, Long SS, eds. *Red Book: 2015 Report of the Committee on Infectious Diseases*. 30th ed. Elk Grove Village, IL: American Academy of Pediatrics; 2015:400–423.

- Recommendations of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition for the management of children with hepatitis C have recently been published.

HEV

- Treatment of HEV infection is supportive.
- A recombinant peptide vaccine has been developed and seems to be safe and highly effective in a high-risk population.

AIH

- Prednisone is a potent anti-inflammatory agent usually used as first-line therapy in AIH.
- Because of its side effects, particularly on growth, a second immunosuppressive, azathioprine, is often added.
- This allows a reduction or complete weaning of the prednisone.
- Some patients who are refractory to azathioprine and steroids have responded to cyclosporine 80 or tacrolimus.

Table 5. Recommendations for Hepatitis B Virus Prophylaxis After Percutaneous or Mucosal Exposure to Blood or Body Fluids[a]

	Treatment When Source Is		
Exposed Person	**HBsAg Positive**	**HBsAg Negative**	**Unknown or Not Tested**
Unimmunized	Administer HBIG[b] (1 dose) and initiate HBV vaccine series.	Initiate HBV vaccine series.	Initiate HBV vaccine series.
Previously immunized			
Known responder	No treatment	No treatment	No treatment
Known nonresponder		No treatment	If known high-risk source, treat as if source were HBsAg positive.
After 3 doses	HBIG (1 dose) and initiate reimmunization[c].		
After 6 doses	HBIG: 2 doses separated by 1 month		
Response unknown	Treat exposed person for anti-HBs[d].	No treatment	Test exposed person for anti-HBs[d].
	If adequate, no treatment		If adequate, no treatment
	If inadequate, HBIG × 1 and vaccine booster		If inadequate, vaccine booster dose[e]

Abbreviations: anti-HBs, antibody to HBsAg; HBIG, hepatitis B immune globulin; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus.

[a] Advisory Committee on Immunization Practices, Centers for Disease Control and Prevention. Immunization of health-care personnel: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep*. 2011;60(RR-7):1–45.

[b] Dose of HBIG, 0.06 mL/kg, intramuscularly.

[c] The option of giving 1 dose of HBIG (0.06 mL/kg) and reinitiating the vaccine series is preferred for nonresponders who have not completed a second 3-dose vaccine series. For people who previously completed a second vaccine series but failed to respond, 2 doses of HBIG (0.06 mL/kg) are preferred, 1 dose as soon as possible after exposure and the second 1 month later.

[d] Adequate anti-HBs is ≥10 mIU/mL.

[e] The person should be evaluated for antibody response after the vaccine booster dose. For people who receive HBIG, anti-HBs testing should be performed when passively acquired antibody from HBIG is no longer detectable (eg, 4–6 months); for people who did not receive HBIG, anti-HBs testing should be performed 1 to 2 months after the vaccine booster dose. If anti-HBs is inadequate (<10 mIU/mL) after the vaccine booster dose, 2 additional doses should be administered to complete a 3-dose re-immunization series, followed by postimmunization testing for anti-HBs and HBsAg.

From American Academy of Pediatrics. Hepatitis B. In: Kimberlin DW, Brady MT, Jackson MA, Long SS, eds. *Red Book: 2015 Report of the Committee on Infectious Diseases.* 30th ed. Elk Grove Village, IL: American Academy of Pediatrics; 2015:400–423.

- Prednisone is begun at a dosage of 2 mg/kg/d (maximum 60 mg daily).
- When evidence of improvement is seen, the prednisone dosage may be tapered at weekly intervals to a dosage that achieves and maintains clinical and biochemical evidence of improvement.
- Toxicity of azathioprine (eg, hematopoietic toxicity) must be monitored for, particularly in patients with thiopurine S-methyl-transferase deficiency.
- The latter can be diagnosed by PCR for the major mutations or by assays of enzyme activity.
- In addition, adequacy of thiopurine exposure and avoidance of toxicity may be determined by measuring thiopurine metabolites where available.
- Remission is defined as
  - Absence of clinical symptoms
  - Aminotransferase level no more than 2 times normal
  - Decreasing serum gamma globulin levels
  - Resolution of the aggressive histologic appearance on a liver biopsy specimen

- Duration of therapy once remission is achieved is controversial.
  - Generally, once remission is achieved, steroids may be tapered gradually.
- Long-term treatment with a low-dose steroid or azathioprine is often required.
- Remission generally occurs as follows:
  - Clinical remission: within 3–6 months
  - Biochemical remission: within 6–12 months
  - Histologic remission: within 12–24 months
- During the steroid taper, the patient must be watched at 2- to 4-week intervals for ~3 months for evidence of early recurrence, and then the frequency of observation can be decreased.
- At least 80% of children seem to achieve initial remission.
- Although relapses are common, long-term control is usually achieved with continuous immunosuppressive therapy.
- The child with AIH and fulminant hepatic failure poses a difficult therapeutic problem.
  - Prednisone and azathioprine have been used in this situation with success.
  - However, liver transplantation may be necessary for survival.
- Most children with chronic active hepatitis are likely to have a prolonged survival on minimal long-term immunosuppression.

Drug-Induced Hepatitis

- Profound effects of acetaminophen toxicity can be treated with IV *N*-acetylcysteine.
- In all other cases of suspected drug-induced hepatitis, supportive care is recommended along with discontinuation of the suspected drug.

Metabolic Liver Disease

- Aim of therapy in Wilson disease is copper chelation in a controlled manner.
  - First-line therapy is penicillamine in most cases.
    - Requires close monitoring for significant side effects, including allergies and renal disease
  - Triethylene tetramine hydrochloride (trientine) has been effective in the same dose as penicillamine.
    - Associated with milder side effects
  - Tetrathiomolybdate in a more stable form is now available and may be the preferred treatment for neurologic Wilson disease with better control of free serum copper.
  - Zinc may be used as initial therapy in patients without clinical disease who are diagnosed incidentally on family screening.
- No specific therapy is available for α_1 AT deficiency.
  - Liver transplantation should be considered for end-stage liver disease.
  - Carbamazepine was shown in a mouse model to decrease the hepatic load of mutant α_1 AT protein and improve fibrosis and is undergoing evaluation in humans.
- Dietary restriction of galactose is the treatment of choice for galactosemia.
- Tyrosinemia may be treated with a phenylalanine and a tyrosine-restricted diet together with nitisinone ([2-nitro 4-trifluoromethyl benzoyl]-1,3-cyclohexanedione).
  - Nitisinone is an inhibitor of an early enzyme in the tyrosine degradation pathway that is thought to prevent the accumulation of toxic products, resulting in clinical improvement in most patients.
  - Although costly, nitisinone has been proposed as an alternative to liver transplantation.
  - Whether it will decrease the risk of hepatocellular carcinoma is not yet determined.
- Bile acid–replacement therapy is the treatment of choice for inborn errors of bile acid synthesis.
- PFIC 1, 2, and 3
  - No specific therapy apart from supportive treatment.
  - Liver transplantation may be required for end-stage liver disease.
- Ursodeoxycholic acid may be used in the treatment of liver disease secondary to cystic fibrosis and may halt disease progression.

Fulminant Hepatic Failure

- Needs to be managed in a setting with liver transplantation expertise.
- Requirements of liver support must be balanced with management of fluids, nutrition, and encephalopathy.
- Transferring a child with severe hepatitis early before the need for intensive care management is preferable.

Liver Transplantation

- Has improved mortality and morbidity of children who have severe liver disease.
- Indications include
  - Liver failure
  - Growth failure
  - Intractable itch from cholestasis
- Pretransplant management involves aggressive nutritional therapy and prevention of complications, such as bacterial peritonitis and variceal hemorrhage.

- Transplantation for chronic liver failure secondary to HBV infection is complicated by almost 100% recurrence of infection.
  - HBIG followed by lamivudine improves the outcome.
- Recurrence of HCV infection after transplantation is ~90%, but transplantation is recommended because recurrent disease is usually mild.
- Liver transplantation for all causes results in 5-year survival rates in children approaching 70%–80%.
- Focus is directed toward improving morbidity related to immunosuppressive medications and quality-of-life issues.

WHEN TO ADMIT

- Prolonged prothrombin time (>4 seconds over control) or INR >1.5 in a child with severe hepatitis of any cause
- Acute encephalopathy in a child with severe hepatitis of any cause
- Dehydration requiring IV fluid resuscitation in a child with severe hepatitis
- Gastrointestinal bleeding in a child with acute or chronic hepatitis

WHEN TO REFER

- Children with fulminant liver failure of any cause should be promptly referred to a specialist affiliated with a pediatric liver transplant center.
- Children with uncomplicated hepatitis A can usually be managed by a general pediatrician.
  - However, children with chronic hepatitis B, C, or D should be referred to a pediatric gastroenterologist or infectious disease specialist.
- Children with metabolic liver disease, drug-induced hepatitis, or AIH should be referred to a pediatric specialist in metabolic disease or gastroenterology.
- Fulminant hepatic failure, defined as a lack of a preexisting liver disease and severe impairment of hepatic function as evidenced by prolonged prothrombin time (>4 seconds over control) that is unresponsive to large doses of vitamin K.
- Any of the following conditions:
  - HBsAg-positive serologic test in children 1 year of age *or*
  - Anti-HCV positive serologic test in children 3 years of age *or*
  - Any diagnosis of drug-induced hepatitis (unexplained elevation of serum aminotransferases or bilirubin in a child who is taking or has recently taken any medication).
- Any diagnosis of metabolic liver disease (unexplained elevation of serum aminotransferases or bilirubin in a child) and a positive screening test.
  - Low ceruloplasmin
  - Low galactose-1-phosphate uridyl transferase
  - Positive urine-reducing substances

FOLLOW-UP

- HBV
  - Although the best methods and frequency of surveillance have not been determined, careful follow-up includes
    - Serial serum α-fetoprotein measurement
    - Ultrasonography of the liver

COMPLICATIONS

- HBV
  - Long-term effects of acquiring HBV in infancy include cirrhosis and hepatocellular carcinoma.
  - Many cases of HBV-related liver cancer have been described in children.
  - Most cases of HBV-related hepatocellular carcinoma occur in adults.
  - Recent studies suggest that perinatal transmission is important in hepatocarcinogenesis, perhaps related to the high dose of HBV DNA with subsequent tolerance and persistent necroinflammatory activity.
  - The genotype of the virus may correlate with natural history, response to therapy, and risk of developing hepatocellular carcinoma.
- HCV
  - Fibrosis increases with duration of infection but in an unpredictable manner.
  - Patients with chronic HCV infection who become infected with HAV are at substantial risk of fulminant hepatic failure.
  - Chronic HCV infection predisposes patients to cirrhosis and hepatocellular carcinoma over 20 years in those with adult-acquired infection.
  - The natural history of perinatally acquired HCV infection is still under evaluation.

PREVENTION

- HAV
  - Vaccination routinely after 1 year of age and in all adolescents
- HBV
  - Aggressive immunization programs have substantially lowered vertical and horizontal transmission rates, as well as the average annual incidence of hepatocellular carcinoma.

- HCV
  - Maternal-fetal transmission has been linked to in utero monitoring and prolonged rupture of membranes.
    - HCV does not appear to be prevented by cesarean delivery.
  - Although HCV RNA has been detected in human milk, current evidence suggests that breastfeeding is not contraindicated.
    - In developed countries, mothers should consider abstaining from breastfeeding if nipples are cracked and bleeding.
  - Patients with HCV infection should be counseled to avoid hepatotoxic medications and alcohol and should receive vaccination against HAV and HBV infections to prevent additional liver damage.

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2. Modified from Centers for Disease Control and Prevention. A comprehensive immunization strategy to eliminate transmission of hepatitis B virus infection in the United States: recommendations of the Advisory Committee on Immunization Practices (ACIP). Part II: immunization of adults. *MMWR Recomm Rep.* 2006;55(RR–16):1–33

DEFINITION

- Hepatomegaly is enlargement of the liver, resulting from an increase in the number or size of cells and structures within the liver.
  - Usually manifests clinically as a palpable liver.
  - Not all palpable livers result from hepatomegaly.

HISTORY

- Describe the hepatomegaly.
  - Timing of onset
  - Associated signs/symptoms
- Review of systems.
  - Gastrointestinal symptoms (eg, abdominal pain, vomiting, hematemesis, color of stools).
  - Pulmonary manifestations (eg, dyspnea, hyperinflation, tracheal deviation).
  - Cardiac manifestations (eg, cough, chest pain).
  - Neuropsychiatric symptoms.
  - History of trauma.
  - Assess the likelihood of hypercoagulability.
  - Exposure to toxins and medications.
- Medical history.
  - Infectious exposures
  - Asthma
  - Cardiac disease
  - Medication history
- Perinatal history.
  - Jaundice
- Family history.
  - Inflammatory conditions (eg, systemic lupus erythematosus, sarcoidosis)
  - Cancer
  - Metabolic conditions/storage disorders (eg, Wilson disease, glycogen storage disease)

PHYSICAL EXAMINATION

- Vital signs
  - Temperature
  - Heart rate, blood pressure, respiratory rate
- Physical examination
  - Liver.
    - Determine size/span.
      - Estimation of liver span correlates more strongly with hepatomegaly than projection below the costal margin.
      - Determine the upper margin by percussion.
      - Determine the lower margin by percussion or palpation; palpate upward from iliac crest.
      - The upper edge of liver dullness is usually at the level of the fifth rib in the right midclavicular line.
      - Normal span ranges from 5.9 cm in the first week of life to 6.5–8 cm by 15 years of age.
    - Determine characteristics.
      - Firm and tender suggests an acute inflammatory disorder.
      - A hard liver may be neoplastic.
      - Smooth and exquisitely tender liver may result from vascular distention.
    - Auscultate for bruits.
  - Spleen.
    - An enlarged spleen with a palpable liver usually suggests significant disease.
  - Assess other systems.
    - Ocular: Look for Kayser-Fleischer rings.
    - Respiratory: Examine for evidence of hyperinflation.
    - Cardiovascular.
      - Examine for evidence of congestive heart failure.
      - Examine for evidence of cardiac tamponade (eg, pulsus paradoxus).
    - Skin: Assess for jaundice and evidence of trauma.

DIFFERENTIAL DIAGNOSIS

- Infectious/inflammatory hepatitis
  - Viral
  - Bacterial (eg, abscess, sepsis)
  - Toxic (eg, drugs, including acetaminophen)
  - Neonatal
  - Autoimmune (eg, systemic lupus erythematosus, sarcoidosis)
- Neoplastic/infiltrative disorders
  - Primary tumors
    - Hepatoblastoma
    - Hepatocellular carcinoma
    - Hemangioma
    - Focal nodular hyperplasia
  - Metastases
    - Lymphoma
    - Leukemia
    - Neuroblastoma
    - Wilms tumor
    - Histiocytosis
- Storage disorders
  - Fat accumulation
    - Obesity
    - Malnutrition
    - Reye syndrome
    - Cystic fibrosis
    - Type 2 diabetes mellitus

- — Lipid infusion
- — Metabolic liver disease
- — Lipidoses (eg, Niemann-Pick, Gaucher, Wolman diseases)
- Glycogen excess
  - — Glycogen storage disease
  - — Infant of mother who has diabetes
  - — Beckwith-Wiedemann syndrome
  - — Total parenteral nutrition
- Copper accumulation
  - — Wilson disease
  - — Indian childhood cirrhosis
- Miscellaneous
  - — α_1-Antitrypsin deficiency
  - — Hypervitaminosis A

■ Vascular congestion
- Suprahepatic
  - — Congestive heart failure
  - — Cardiac tamponade
  - — Constrictive pericarditis
- Intrahepatic
  - — Hepatic vein thrombosis (Budd-Chiari syndrome)
  - — Hepatic vein web
  - — Vascular malformations
    - ■ Cavernous hemangioma
    - ■ Capillary hemangioma
    - ■ Hemangioendothelioma

■ Biliary obstruction
- Congenital biliary atresia
- Congenital hepatic fibrosis
- Caroli disease

■ Displaced or prominent liver edge, without true hepatomegaly
- Downward displacement of the right hemidiaphragm
  - — Hyperinflated lung (eg, asthma, bronchiolitis, pneumonitis)
  - — Tension pneumothorax
  - — Congenital diaphragmatic hernia
  - — Thoracic tumors
- Subdiaphragmatic lesions (eg, abscess)
- Aberrant lobe of liver

LABORATORY EVALUATION

■ Evaluation is directed toward the suspected cause; thus, laboratory work is not always indicated.

■ Possible tests include
- Liver enzymes (aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, γ-glutamyl transferase)
- Liver function studies (prothrombin time, international normalized ratio, partial thromboplastin time, albumin, total protein, ammonia)
- Fractionated bilirubin
- Toxin screens, including acetaminophen, aspirin
- Complete blood cell count, peripheral blood smear
  - — Hemolytic anemia may indicate Wilson disease.
- Hepatitis panel
- Blood cultures
- Vitamin A level
- Copper studies
- Tumor markers

IMAGING

■ Imaging studies are determined by clinical suspicion.

■ Imaging can help to assess liver size.
- Radiography
- Ultrasonography
  - — May help to identify liver masses, abscesses
- Computed tomography (CT), magnetic resonance imaging, sulfur colloid scintigraphy
  - — Define masses detected on ultrasonography.
- Hepatic angiography
  - — May be indicated to evaluate suspected vascular tumors

DIAGNOSTIC PROCEDURES

■ Percutaneous liver biopsy
- Can be used to confirm some metabolic and genetic disorders
- Idiopathic neonatal hepatitis
  - — Marked infiltration with inflammatory cells
  - — Giant-cell transformation
- Biliary atresia
  - — Bile duct proliferation
  - — Giant-cell transformation
- Congenital hepatic fibrosis
  - — Diffuse periportal and perilobular fibrosis on histologic analysis

■ Percutaneous liver aspiration
- Often performed under ultrasound or CT guidance
- Confirms liver abscess and allows sampling of organisms for culture

TREATMENT APPROACH

■ Treatment is aimed at the underlying disease entity.

SPECIFIC TREATMENT

Inflammatory Disease

- Inflammatory hepatitis
  - Supportive care
- Bacterial infection
  - Appropriate antimicrobial agents

Liver Tumors

- Surgical excision.
- Chemotherapy may be a helpful adjunct in reducing tumor size preoperatively or postoperatively.

Biliary Atresia

- Extrahepatic.
  - Surgical correction
- Intrahepatic.
  - Portoenterostomy (Kasai operation)
- Patients who develop cirrhosis and portal hypertension require liver transplantation.

Other Disorders

- Metabolic or genetic disorders
  - Dietary modifications.
  - Gaucher disease: imiglucerase, a new synthetic enzyme.
  - Wilson disease: D-penicillamine chelation therapy, with zinc acetate for maintenance therapy.
  - Glycogen storage disorders.
    - Frequent small feedings of a high-protein, complex-carbohydrate diet
    - Continuous nighttime feeding via gastrostomy tubes
  - Other recombinant glucosylceramidases recently approved or pending approval have been proved effective in treatment of Gaucher disease.
    - Velaglucerase alfa (Shire HGT)
    - Taliglucerase alfa (Protalix Biotherapeutics)
- Indian childhood cirrhosis
  - Chelation therapy with D-penicillamine reduces mortality significantly if administered early in the disease course.

Liver Failure/Cirrhosis

- Biliary atresia
  - Even with surgical treatment, many patients develop cirrhosis and portal hypertension, requiring liver transplantation.
- Autoimmune and toxic hepatitis
  - With intractable liver failure, liver transplantation is indicated.

WHEN TO REFER

- With concomitant splenomegaly
- Liver with hard consistency
- With distended abdominal veins
- Audible bruit over the liver
- Suspicion of cancer

WHEN TO ADMIT

- Liver failure
- Impending liver failure

DEFINITION

- Human herpesvirus, or herpes simplex virus (HSV)
  - DNA virus with a protein coat.
  - One of the most common agents infecting humans.
  - Although 85%–95% of primary infections may be asymptomatic, in certain circumstances, the disease can be fatal.
  - Can be divided definitively into 2 immunologic types that correlate with clinical manifestations.
    - Human herpesvirus (herpes simplex virus) 1 (HSV-1): tends to be associated with disease above the waist
    - Human herpesvirus (herpes simplex virus) 2 (HSV-2): associated with disease below the waist, with sexually related transmission, or with disease acquired neonatally

SIGNS AND SYMPTOMS

- General
  - Incubation period of 2–12 days
  - Primary infection, if apparent, is usually heralded by
    - Classic herpetic enanthema or exanthem
      - Lesions are painful vesicles, usually several millimeters in diameter, on an erythematous base.
    - Constitutional symptoms
      - Malaise
      - Fever
      - Anorexia
      - Irritability
  - Recurrent episodes
    - Similar vesicular eruption in the same general anatomic area as the primary eruption but without concomitant constitutional symptoms
- HSV-1
  - Acute gingivostomatitis
    - The most common form of HSV-1 seen in children.
      - 10% of cases are caused by HSV-2.
    - Peak incidence is between 6 months and 5 years of age.
    - Characterized by abrupt onset of fever, irritability, and poor feeding.
    - 1–2 days later.
      - Very tender, red, friable mucous membranes surrounding 2- to 3-mm white ulcerations
      - Severe halitosis
    - Vesicular stage is rarely seen.
    - Large, tender anterior cervical and submandibular lymphadenopathy is common.
    - Duration of illness from 5–14 days.
    - Severity ranges from mild to so severe that oral intake becomes negligible, and hospitalization for intravenous (IV) hydration may be required.
    - Bacteremia caused by *Kingella kingae,* part of the normal flora of the mouth, has been observed in a few cases; speculated to progress to focal skeletal infection, such as osteomyelitis.
  - Herpes labialis (cold sores)
    - Crust and heal without scarring in 7–10 days.
    - May be found on the upper or lower lip.
    - Most commonly seen on the vermilion border and adjacent skin of the lips, although lesions can occur on the chin, cheeks, and around the nose.
    - Recurrence at the same site is extremely common.
  - Herpetic whitlow (herpetic paronychia)
    - Extremely painful condition involving herpetic infection of a digit.
    - Result of inoculation at the site of local trauma.
    - May occur as a result of autoinoculation in children with orofacial herpes; common in thumb-suckers.
    - Although the sore may resemble a bacterial paronychia, it should not be incised.
    - Sometimes associated with systemic symptoms, such as fever and malaise, especially in infants.
    - Lesion typically contains clear fluid in the initial stage that may become cloudy after a week due to accumulation of white blood cells in the lesion.
    - The disease usually subsides completely within 3 weeks.
  - Ocular herpes
    - One of the most common causes of corneal blindness in the United States.
    - HSV-1 has much greater association with ocular pathology than HSV-2.
    - HSV-1 can manifest as conjunctivitis, iridocyclitis, acute retinal necrosis, and keratitis.
    - Primary infection usually involves acute keratoconjunctivitis with intense swelling of the lids but without exudates.
    - Typical herpetic vesicles are often found on the skin surrounding the involved eye.

- Recurrent disease
  - Can be even more severe.
  - May involve superficial or deep epithelial ulceration, stromal damage, or uveitis.
- Should always be referred to an ophthalmologist for care.
- The use of topical steroid preparations in a probable case of ocular herpes can have devastating consequences.

- Herpes and sports/herpes gladiatorum
  - Transmission usually takes place via skin-to-skin contact thorough areas of skin breakdown.
  - Condition usually is benign and self-limited.
  - The face is the most common site of infection among wrestlers.
  - Complications include ocular involvement (blepharitis, follicular conjunctivitis, keratitis, scleritis, and uveitis).
    - Described in ≤8% of players in wrestling camps.
    - Dendritic keratitis with subsequent corneal scarring may lead to permanent blindness.

- HSV-2
  - Usually exhibited by typical herpetic vesicles on
    - Penile shaft, prepuce, or glans penis in the male patient
    - Labia minora or majora, mons, nearby skin, or within the vagina in the female patient
  - Primary infection is accompanied by
    - Significant local pain, burning, or paresthesia
    - Constitutional symptoms of fever and malaise, dysuria, and inguinal lymphadenopathy
  - Recurrent bouts are less severe than initial occurrences.
- Neonatal herpes
  - Presentation is nonspecific, at least initially.
  - Presentation is usually acute, occurring in the first week or so of life, uncommonly as late as 3 or 4 weeks of age.
  - Symptoms may include
    - Poor feeding, vomiting, fussiness or lethargy, fever or hypothermia, jaundice, and hepatosplenomegaly.
    - Seizures, cyanosis, and apnea may occur.
  - Most neonates, though notably not all, who have neonatal herpes eventually demonstrate a vesicular rash as individual lesions or clumps of vesicles.
  - Classically classified into 3 categories based on clinical manifestations.
    - 25% of neonates with neonatal HSV have disseminated disease involving visceral organs with or without central nervous system (CNS) involvement.
      - In disseminated infection, the liver and lungs tend to be most involved, and hepatoadrenal necrosis is virtually always found.
    - 30% of neonatal infections are seen in neonates with CNS abnormalities without involvement of viscera.
    - In 45% of cases, the neonate's skin, eyes, or mouth (SEM) are involved but not the CNS or viscera.

DIFFERENTIAL DIAGNOSIS

- HSV-1
  - Coxsackievirus A herpangina.
    - Most common ulcerative enanthema to be considered
    - Results in lesions very similar in appearance to HSV
    - Located in the posterior oral cavity, unlike the anterior localization of herpetic lesions
  - Other infections include
    - Varicella
    - Cytomegalovirus
    - Syphilis
  - Differential diagnosis for herpes gladiatorum.
    - Localized bacterial, viral, or fungal infections, such as impetigo, molluscum, and tinea.
    - A critical difference is the extensive regional adenopathy observed in herpes gladiatorum and the propensity of these lesions to cross the hairline onto the scalp.
  - Autoimmune diseases, such as
    - Behçet syndrome
    - Reiter syndrome
    - Inflammatory bowel disease
  - Systemic lupus erythematosus and cyclic neutropenia
    - Might be considered in a broader differential diagnosis.
    - Cultures for herpes can confirm the final diagnosis if necessary.
  - Neonatal HSV disease must always be considered in a newborn with a skin rash ranging from vesiculopapular to vesiculoulcerative.

LABORATORY FINDINGS

- HSV-1
  - Clinical diagnosis rarely requires a laboratory confirmation.
- HSV-2
  - Viral culture
    - In general, the most sensitive method of diagnosis.
    - Requires several days for definitive result, depending on the size of the inoculum.
    - Vesicles, stool, urine, and mucosal surfaces may be used as sites to obtain culture sample.
  - Direct detection methods, including fluorescent antibody and immunoperoxidase assays
    - Can be used when lesions are available for scraping.
    - Test results are rapid but have lower sensitivity.
    - Viral culture is required for confirmation of a negative finding.
  - Tzanck test and Papanicolaou stains
    - Neither is sufficiently specific nor sensitive to serve as a screen for HSV.
  - Polymerase chain reaction (PCR)
    - Highly specific and sensitive.
    - Can discriminate between HSV-1 and HSV-2 in cerebrospinal fluid.
    - The diagnostic method of choice in HSV encephalitis.

TREATMENT APPROACH

- No universal cure exists for herpesvirus infections.
- Acyclovir has become the first-line treatment of choice.
  - Recent work demonstrates some improved mortality with prolonged high-dose (60 mg/kg/d divided every 8 hours) IV acyclovir.
  - Treatment should always begin early when there is suspicion of disease.
    - Early acyclovir therapy (within 1 day after hospital admission) has been associated with a statistically significant lower mortality rate compared with treatment initiated after 1 day (6.6% vs 9.5%).
  - Empiric treatment is recommended, especially given the low risk for serious side effects of acyclovir.
  - Prolonged therapy with oral acyclovir appears to result in improved long-term outcomes.
  - For neonatal HSV survivors with CNS involvement
    - Suppressive therapy with oral acyclovir for 6 months has been associated with improved neurodevelopmental outcomes when compared with placebo.

SPECIFIC TREATMENTS

Recommended Treatment Regimens for Genital Herpes[1]

- First clinical episode
  - Oral antiviral therapy shortens the duration of symptoms and viral shedding.
  - Indicated for a ≥10-day course.
  - If begun within 1 day of onset of the first lesion, episodic therapy may limit the duration and severity of recurrences.
    - Acyclovir 400 mg orally 3 times a day for 7–10 days (max dose in children at 80 mg/kg/24 h divided every 6 to every 8 hours) *or*
    - Famciclovir 250 mg orally 3 times a day for 7–10 days *or*
    - Valacyclovir 1 g orally twice a day for 7–10 days.
    - Treatment may be extended if healing is incomplete after 10 days of therapy.
- Episodic therapy for recurrent genital herpes
  - Acyclovir 200 mg orally 5 times a day for 5 days *or*
  - Acyclovir 400 mg orally 3 times a day for 5 days *or*
  - Acyclovir 800 mg orally twice a day for 5 days *or*
  - Famciclovir 125 mg orally twice a day for 3–5 days *or*
  - Valacyclovir 500 mg orally twice a day for 3 days
- Suppressive therapy for recurrent genital herpes
  - Acyclovir 800–1,000 mg a day, divided 2–5 times a day for up to 1 year (max dose in children at 80 mg/kg/24 h divided every 6 to every 8 hours) *or*
  - Famciclovir 250 mg orally twice a day for 1 year (then reassess) *or*
  - Valacyclovir 500–1,000 mg orally once a day for a year, and then reassess for recurrences. Patients with <9 recurrences per year may be dosed at 500 mg/dose orally once a day for a year.

- The same medications have been shown to decrease recurrences by 70%–80% when used as long-term suppressive therapy in patients with particularly severe or frequent recurrences.
  - The cost of therapy may limit its usefulness.
- Therapy for immunosuppressed individuals
  - May warrant hospitalization and the use of IV acyclovir

Other Herpetic Syndromes

- Herpetic gingivostomatitis
  - Oral acyclovir
    - Can shorten the duration in children by 6 days if begun within the first 72 hours of illness.
    - Potential for significant cost savings because of the frequent need for IV hydration.
    - Only modest efficacy has been shown with treatment of episodic oral herpes.
    - Topical antiviral therapy for recurrences has been demonstrated to decrease duration of symptoms by ≤1 day.
- Ocular conditions
  - Topical antivirals are used to treat superficial keratitis.
  - Oral acyclovir may be beneficial in situations of recurrent ocular lesions.
- Herpes gladiatorum
  - Oral antivirals have been shown to prevent herpes gladiatorum at wrestling camps.
- Herpes encephalitis
  - IV acyclovir remains the mainstay of treatment.
  - Acyclovir has significantly decreased mortality but has only modestly affected morbidity.
  - Therapy must be initiated promptly to ensure the most favorable outcome.
    - Early treatment has improved prognosis but is most effective when begun before the onset of loss of consciousness.
  - For infants <3 months
    - Treatment should be continued for ≥21 days.
  - For infants and children ≥3 months
    - Treatment should last 14–21 days.

WHEN TO ADMIT

- Neonates and infants with suggested or confirmed neonatal herpes
  - Must be carefully monitored and treated with IV acyclovir
- All individuals thought to have herpes encephalitis
  - Must be hospitalized and treated expectantly with IV acyclovir
- Immunosuppressed individuals with herpes infections
  - May require IV antiviral therapy and will require hospitalization

WHEN TO REFER

- All neonates who are thought to have neonatal herpes
  - Should be considered potentially critically ill.
  - Would benefit from subspecialty involvement to include critical care, neonatology, infectious disease, and others as indicated.
- Regardless of age, patients who have known or suggested immunosuppression
  - May benefit from subspecialty consultation.
- Ocular herpes should always be referred to an ophthalmologist.
- Children in whom ocular steroid therapy is considered may benefit from ophthalmologic consultation to rule out possible ocular herpes infection.

COMPLICATIONS

- HSV-1
  - Certain human hosts are at more serious risk than others for contracting or developing severe disease.
  - Individuals who may be more likely to show serious disseminated disease are those who
    - Have deficiencies in cell-mediated immunity
    - Are undergoing immunosuppressive therapy for cancer or transplantation
    - Are extremely malnourished
  - Eczema herpeticum is a severe form of a superimposed HSV skin infection in a patient with existing atopic dermatitis or other chronic skin diseases.
    - Varies in severity from mild to fatal.
    - Constitutional symptoms, such as fever and malaise, are the rule.
    - Lesions mostly appear on the head, neck, and trunk, are vesicular, and seem to be at the same stage.
    - Wide areas of skin can become denuded.
    - Enormous fluid, protein, and electrolyte losses are potentially life-threatening.
    - Secondary bacterial infection may complicate the condition.
    - Recurrences tend to be milder than the initial infection.

- Sporadic, fatal encephalitis
  - HSV-1 is considered the most common cause.
  - 2 peaks of illness—first between 6 months and 20 years of age and second in patients >50 years.
  - 250–500 cases per year.
  - Characterized by fever and personality change and often involves seizures.
  - A rapidly progressive encephalopathy culminates in death in 1–2 weeks in >70% of untreated cases.
  - Most patients who survive have significant neurologic morbidity.
    - Many develop developmental delay, behavioral impairment, language disturbance, focal motor deficits, and epilepsy that is often difficult to control.
  - Infection is most often localized to the frontotemporal area, with symptoms and signs of aphasia, personality changes, and focal seizures.
  - HSV DNA by PCR in cerebrospinal fluid is the most sensitive test to confirm diagnosis.
  - Treatment is most effective when initiated early in the course of the disease.

PROGNOSIS

- Prognosis for the many syndromes of HSV has improved greatly with currently available therapies.
- Neonatal herpes.
  - Neonates with disseminated disease involving visceral organs with or without CNS involvement
    - Most likely to die (>80% without treatment and 31% with high-dose treatment).
    - Neonates with HSV-1 disseminated infection have poorer outcomes than those with HSV-2 infection.
    - Aspartate aminotransferase elevation >10× the upper limit of normal shown to be a poor prognostic sign.
    - Hepatoadrenal necrosis is virtually always found.
    - Microcephaly, hydrocephalus, intellectual disability, or seizures occur in many survivors.
  - Neonates with CNS abnormalities without involvement of viscera
    - Without antiviral therapy, mortality >50% and morbidity >90%.
    - With appropriate antiviral therapy, mortality has decreased to 6%, but morbidity remains high.
    - Long-term outcomes include developmental delay, epilepsy, blindness, or cognitive disabilities.
  - Neonates whose SEM are involved but not the CNS or viscera
    - Neonates who had SEM involvement before antiviral drugs became available
      - Were not expected to die.
      - Only 20%–30% were left neurologically impaired.
      - However, many who appeared to have SEM involvement went on to develop disseminated or CNS involvement and to suffer disastrous consequences.

PREVENTION

- HSV-1
  - Decrease in HSV-1 is hypothesized to be related to improved hygiene, which has led to delayed (or possibly reduced) exposure to the virus.
- Neonatal herpes
  - Current guidelines for managing labor in women with a history of genital herpes.
    - Cesarean delivery is not recommended in women with a history of HSV infection without active genital disease during labor.
    - Expeditious cesarean delivery is recommended if active genital lesions are present at the time of delivery or symptoms that might indicate imminent outbreak, such as vulvar pain or burning, are present.
    - Unclear if risks associated with preterm birth outweigh risks of HSV infection in women with premature rupture of membranes.
    - Scalp electrodes should be avoided when active genital HSV infection is suspected in the mother.
  - Joint guidelines to decrease the likelihood of postpartum herpes infection in the neonate (American Academy of Pediatrics and American College of Obstetricians and Gynecologists).
    - Specify isolation criteria to protect healthy neonates from their HSV-infected mothers, other infected neonates, or infected staff.
    - Recommend that women with active recurrent genital herpes ≥36 weeks' gestation should be offered suppressive viral therapy.
      - Limited scientific efforts to support this plan

- Neither routine antepartum genital HSV cultures in asymptomatic patients with recurrent disease nor routine HSV screening of pregnant women is recommended.

REFERENCE

1. Derived from Engorn B, Flerlage J. *The Harriet Lane Handbook.* 20th ed. Philadelphia, PA: Elsevier Saunders; 2015:670–671, 781, 968–969

Hirsutism, Hypertrichosis, and Precocious Sexual Hair Development

DEFINITION

- Hirsutism: presence of excessive terminal hair in androgen-dependent and male pattern areas (especially in females)
- Hypertrichosis: excess hair growth, not limited to androgen-sensitive areas
  - Can be generalized or localized
- Pubarche: onset of sexual hair noted on clinical examination
- Adrenarche: biochemical rise of adrenal androgens
  - Premature adrenarche: <8 years in girls or <9 years in boys
- Hyperandrogenism: presence of elevated androgens
  - Manifested clinically by hirsutism, virilization, acne, or male-patterned baldness
- Premature central precocious puberty (CPP): <8 years in girls and <9 years in boys
- Hair types
  - Lanugo (hair sheds during fetal life)
  - Vellus (fine, short, usually lightly pigmented or nonpigmented)
  - Terminal (thicker, longer, and pigmented; found on the scalp, eyebrows, and eyelashes from the time of birth)
- Hair growth cycles
  - Growth (anagen phase; 8%–85% of the cycle; determines the length and diameter of hair)
  - Rapid involution (catagen phase)
  - Resting (telogen phase)

HISTORY

- Patient history
  - Current age
  - Ethnicity
  - History of weight change
  - Height acceleration
- Hair growth description
  - Age of onset
  - Progression of hair growth
  - Location/distribution of hair
- Presence of other premature/abnormal pubertal features
  - Body odor
  - Irregular menses
- Medical problems
  - Neurologic conditions
  - Developmental history
- Medications
  - Exposure to exogenous sources of androgens
- Birth history
  - Birth weight/length
    - Special attention to personal or family history of small for gestational age (SGA) neonate
  - Perinatal problems
- Family history
  - Maternal polycystic ovary syndrome (PCOS)
  - Early infant demise
  - Hirsute or infertile female relatives

PHYSICAL EXAMINATION

- Presenting symptoms and signs
  - Preadolescent: body hair or odor
  - Adolescent females
    - Menstrual irregularities
    - Dermatologic manifestations of hyperandrogenism (eg, severe acne, hirsutism, androgenic alopecia)
  - Adolescent males come to attention much less frequently, unless
    - Virilization is rapidly progressive.
    - Clinical signs, such as alopecia or acne, are excessive.
- General
  - Blood pressure
  - Anthropometric measurements
  - Dysmorphology
  - Masculinization
- Skin
  - Acne, oily skin
  - Café au lait spots, striae
- Hair
  - Type
    - Lanugo
    - Vellus
    - Terminal
  - Amount/severity
  - Location/pattern
    - Androgen-dependent areas
    - Generalized
- Thyroid enlargement
- Puberty
  - Tanner stage pubic hair
  - Females
    - Breast Tanner staging
    - Areolar hair
    - Clitoromegaly
    - Vaginal mucosa (estrogenization)
  - Males
    - Testicular volume
    - Phallic enlargement

- Modified Ferriman-Gallwey score
  - Widely accepted method of quantifying hirsutism.
  - Estimates the amount of terminal hair in 9 areas: upper lip, chin, arms, thighs, chest, and upper and lower abdomen and back.
  - Each area is assigned a score of 0 (absent) to 4 (extensive hair growth visible).
    - Total score can range from 0–36.
    - Score ≥8 indicates hirsutism.
    - Score 8–15 indicates moderate hirsutism.
    - Score >15 indicates severe hirsutism.
  - Limitations of the Ferriman-Gallwey score.
    - Subjective assessment
    - Inability to account for focal hirsutism
    - Lack of population-based data that take into account racial and ethnic differences in body hair

DIFFERENTIAL DIAGNOSIS

- History and physical examination will guide further evaluation and separate benign conditions from more serious pathology.
- The differential diagnosis of premature pubarche is age dependent and may be the presenting sign of a more serious underlying endocrinopathy.

Hypertrichosis

- Differentiate between true sexual hair and hypertrichosis.
  - Sexual hair: dark, coarse, terminal hair limited to androgen-dependent regions
  - Hypertrichosis: excess hair growth relative to age, sex, and ethnicity but excluding androgen-induced hair growth
- Diagnosis is based on
  - Type of hair (lanugo, vellus, or terminal)
  - Age of onset (congenital or acquired)
  - Distribution (generalized or circumscribed)
  - Location (forehead, ear, neck, back)
    - Localized lumbosacral hypertrichosis in a newborn should trigger a search for an occult spinal dysraphism.
- Rare in children but has many causes and associated conditions.
  - Congenital/genetic disorders
    - Congenital hypertrichosis lanuginose
      - Generalized homogeneous lanugo hair over the entire body which progressively sheds over the first year of life
    - Universal congenital hypertrichosis/Ambras syndrome
      - Extremely long vellus hair growth over the entire body, except palms, soles, and mucosae
    - Mucopolysaccharidosis
    - De Lange syndrome
    - Trisomy 18
    - Fetal hydantoin syndrome
    - Fetal alcohol syndrome
  - Systemic illness
    - Anorexia nervosa
    - Hypothyroidism
    - Malnutrition
    - Malignancies
  - Medications
    - Corticosteroids
    - Diazoxide
    - Phenytoin
    - Cyclosporine
    - Streptomycin
    - Minoxidil

Adrenal Hyperandrogenism

- Premature adrenarche
  - Usually presents with pubic hair.
    - Perilabially in girls
    - Base of the penis in boys
  - Associated findings.
    - Axillary hair and odor, oily skin, or mild acne.
    - Signs of virilization are absent.
    - Transient height acceleration and advancement of bone age may be present.
  - Exposure to an exogenous hormone or drug must be ruled out (eg, family member who is using a testosterone gel without taking proper precautions for close contacts).
  - Premature adrenarche may be the first sign of a serious underlying disorder.
    - Androgen-secreting adrenal tumor.
    - Congenital adrenal hyperplasia (CAH).
    - In these conditions, signs of virilization can be present and bone age is significantly advanced.
- CAH
  - Classic form
    - Usually diagnosed in infancy with salt wasting in boys and ambiguous genitalia plus salt wasting in girls

- Non-classic 21-hydroxylase deficiency
  - Typically presents later in life, with premature adrenarche, hirsutism, or menstrual abnormalities

Gonadal Hyperandrogenism

- Gonadotropin-dependent ("central" or "true") precocious puberty
  - Associated with abnormalities of the central nervous system (CNS).
    - Congenital malformations and tumors
      - Hypothalamic hamartoma: ectopic neural tissue secreting gonadotropin-releasing hormone (GnRH)
    - Trauma, infection, surgery, radiation, or chemotherapy
  - For most affected females, no specific cause of CPP can be identified.
    - Precocity is, therefore, classified as idiopathic.
- Gonadotropin-independent precocious puberty
  - Causes include gonadal tumors, Albright syndrome, and familial testotoxicosis.
  - Peripheral precocious puberty can induce maturation of the hypothalamic-pituitary-gonadal (HPG) axis and secondarily lead to true central precocity.
- Infants
  - In the neonatal period, activation of the HPG axis leads to androgen production peaking at 1–3 months.
    - May cause appearance of pubic hair, usually in atypical locations (eg, on the mons pubis in girls and the scrotum in boys)
    - Generally regresses spontaneously
- Young children
  - Sexual hair is not usually the presenting sign of normal central puberty, but it can precede the initial signs of true puberty in up to 20% of normal boys and girls.
  - Therefore, premature adrenarche may be the presenting sign of premature CPP.
- Adolescent female
  - Differential diagnosis includes PCOS, idiopathic hirsutism, nonclassical CAH, exogenous exposure, or tumor.
- PCOS
  - Menstrual irregularities implying anovulation and clinical or biochemical evidence of ovarian hyperandrogenism are cardinal features.
  - It is imperative to exclude other causes of hyperandrogenism.
    - Exogenous exposure
    - Tumor
    - CAH
    - Other endocrinopathies, such as severe hypothyroidism and hypercortisolism
  - PCOS in adolescents can manifest differently than in adults.
    - An adult woman may report menstrual irregularity or infertility, but an adolescent female might report excess hair, acne, male-pattern alopecia, or menstrual irregularities, including primary amenorrhea.
      - Adolescents with menstrual irregularities or weight gain and acne might be told these findings are normal physiologic changes.
      - This can lead to a delay in medical attention, evaluation, and treatment, as well as a negative effect on self-esteem.
  - Primary amenorrhea and dysfunctional uterine bleeding are possible.
    - Most often, however, the presentation related to menses is oligomenorrhea or secondary amenorrhea.
    - The presence of other findings related to the differential diagnosis of menstrual irregularities should be sought. For example
      - Disordered eating
      - Large weight fluctuations
      - Pregnancy
      - Symptoms of thyroid disease
      - Galactorrhea
  - The tempo of physical change is crucial to determine whether the process is gradual or sudden and rapidly progressive.
    - Sudden changes are more consistent with an exposure or an androgen-secreting tumor.
      - May be accompanied by signs of virilization, including voice deepening and clitoromegaly, which are only rarely seen in PCOS

Idiopathic Hirsutism

- Hirsutism with regular ovulation and normal androgen levels.
- Diagnosis of exclusion.
- Menstrual regularity does not preclude an anovulatory state.

LABORATORY EVALUATION

- If true sexual hair is abnormally present, androgen levels should be measured.
  - Dehydroepiandrosterone
  - Dehydroepiandrosterone sulfate (DHEA-S)
  - Androstenedione
  - Testosterone level
  - 17-hydroxyprogesterone
- Children with premature adrenarche.
  - Androgen levels are in the early pubertal range.
  - Moderate elevation in androgen levels.
    - Adrenocorticotropic hormone stimulation test to exclude nonclassical (or late-onset) CAH
  - Markedly elevated androgen levels.
    - Possible androgen-producing adrenal or gonadal tumor
  - Signs of true pubertal development.
    - Other baseline or stimulation tests to evaluate the HPG axis may be necessary.
- PCOS.
  - Laboratory evaluation will be driven by index of suspicion and whether a previous workup for menstrual irregularities has been performed.
    - Free testosterone is the most helpful test in the diagnosis of PCOS.
    - An alternative is a total testosterone test with sex hormone binding globulin level.
      - Because standard testosterone assays notoriously lack standardization and precision, tandem mass spectrometry should be used if possible.
  - If the patient has not been evaluated in the past, the full complement of studies may include
    - Complete blood cell count
    - Luteinizing hormone
    - Follicle-stimulating hormone
    - Prolactin
    - Thyroid function
    - Pregnancy test
    - Estradiol
    - Chromosomal analysis
    - DHEA-S
    - Androstenedione
    - Insulin
      - Insulin resistance with hyperinsulinism is often seen in PCOS, especially if the patient is obese.
    - Because PCOS is associated with metabolic syndrome, affected patients should be screened for the following glucose and lipid abnormalities:
      - Hemoglobin A_{1c}
      - Fasting glucose
      - 2-hour oral glucose tolerance test
      - Fasting lipid panel
      - Complete metabolic panel

IMAGING

- Ultrasonography or magnetic resonance imaging to localize suspected tumor
- Hypothalamic-pituitary imaging if there are signs of true pubertal development
- Bone age testing (radiograph of left hand and wrist)
  - In children with premature adrenarche, bone age is usually within 2 standard deviations of chronologic age.
  - Accelerated bone age may indicate
    - Nonclassical (or late-onset) CAH
    - Androgen-producing adrenal or gonadal tumor

TREATMENT APPROACH

- Because hypertrichosis is androgen independent, antiandrogen therapies are not indicated for its treatment.
- No specific medical treatment is indicated for premature adrenarche.
- GnRH agonists are the mainstay of treatment for CPP.
- Treatment options for hirsutism include pharmacological therapy and cosmetic management.
  - Education about reasonable expectations is crucial.
  - Effects of pharmacological therapy do not become evident before 6–12 months of treatment because of the long duration of the anagen phase of the hair cycle.
  - Choice of treatment depends on patient preference, the extent to which the area of hirsutism is amenable to cosmetic hair removal, and cost of treatment.
- Metabolic abnormalities should be targeted in adolescents with PCOS and abnormalities of glucose or hyperinsulinism.

SPECIFIC TREATMENT

- Hypertrichosis
  - Counseling about different treatment options based on age, type of hair, and body location
  - Physical cosmetic interventions (See under Cosmetic treatments section.)
  - Light sources and lasers (See under Cosmetic treatments section.)
  - Pharmacologic treatment
    - Because hypertrichosis is not androgen dependent, antiandrogen agents are not indicated.
- Adrenal hyperandrogenism
  - No specific medical treatment is indicated for premature adrenarche.
- Gonadal hyperandrogenism
  - GnRH agonists are the mainstay of treatment for CPP.
- Pharmacologic treatment of PCOS and idiopathic hirsutism
  - Goals.
    - Restoration of menstrual regularity
    - Treatment of hirsutism
    - Treatment of obesity and metabolic abnormalities
    - Improvement of psychological impairment
  - First-line treatment is oral contraceptive pills (OCPs).
    - Products that contain low-androgenic progestins, such as drospirenone or norgestimate, should be used.
    - In addition to decreasing hirsutism, OCPs regulate menstrual cycles and protect the endometrium.
    - If hirsutism persists after 6 months of treatment with an OCP, or if the use of an OCP is contraindicated or not desired, an antiandrogen can be used.
    - In women of childbearing potential, antiandrogen medications should not be used without adequate birth control measures to prevent possible feminization of a male fetus.
  - Spironolactone.
    - The most widely prescribed antiandrogen.
    - Should not be used in patients with renal failure or hyperkalemia or in conjunction with other medications that cause hyperkalemia.
    - Flutamide and finasteride are other antiandrogens used in the treatment of hirsutism.
    - A study comparing spironolactone, flutamide and finasteride demonstrated similar efficacy in treatment of hirsutism after 6 months.
  - Long-term use of pharmacologic therapy for hirsutism in adolescent females has not been studied.
- Cosmetic treatments
  - Hair removal from the skin surface (depilation)
    - Shaving is the least expensive method.
      - Shaving does not increase the diameter of the hair follicle or affect the rate of hair growth.
      - Shaving can cause irritation and folliculitis.
    - Depilatory agents dissolve hair by reducing the disulfide bonds and peptides of hair keratin at the skin surface.
      - They can cause irritant dermatitis.
  - Hair extraction from above the bulb (epilation)
    - Methods include plucking and waxing.
    - Plucking can be painful and time-consuming, making it useful only in small areas, such as the face.
  - Bleaching
    - Camouflages but does not remove dark hair
  - Electrolysis
    - Permanent hair reduction, not removal
    - Involves placing a fine needle in the hair follicle and applying an electrical current
    - Time-consuming and difficult for large areas
  - Photoepilation
    - Permanent hair reduction, not removal.
    - Uses lasers and other light sources, such as intense pulsed light, to damage hair follicles without damaging surrounding tissues.
    - Most effective in patients with light skin complexion and dark hair.
    - Although hair follicles are destroyed, vellus hair follicles can remain and can convert to terminal hair, resulting in hair regrowth.
    - Requires multiple treatments, is expensive, and can cause dyspigmentation and scarring.
  - Eflornithine hydrochloride cream
    - Approved for facial hirsutism
    - Irreversibly inhibits ornithine decarboxylase in hair follicles
    - Can be added to photoepilation therapy for more rapid initial response

- Metabolic abnormalities
  - In adolescents with PCOS who have abnormalities of glucose or significant hyperinsulinism, treatment should be aimed at managing metabolic abnormalities in conjunction with the previously described measures.
  - Dietary and exercise changes should be the first-line treatment for obesity and dyslipidemia.
    - As little as a 5%–10% weight loss can have significant clinical outcomes, including improvement in biochemical hyperandrogenism, menstrual regularity, and glycemic profiles.
    - Set lifestyle changes with small achievable goals.
    - Current evidence suggests that multiple dietary strategies can be successful as long as they are nutritionally adequate and sustainable.
    - Goals for exercise should focus on overall health improvement, not weight loss.
  - Glucophage, a biguanide insulin sensitizing agent, is the single oral antihyperglycemic drug approved for use in children as young as 10 years.
    - Start at a low dose, titrating upward as tolerated, and taking it with meals.
    - Contraindicated with renal or hepatic impairment, severe congestive heart failure, or history of alcohol abuse.
    - Used with OCPs in the treatment of PCOS, especially in patients with diabetes or impaired glucose tolerance.
    - In patients in whom OCPs are contraindicated or not desired, Glucophage has been used as monotherapy.

WHEN TO REFER

- Signs of adrenarche (pubic hair, axillary hair, or odor).
  - <8 years in girls
  - <9 years in boys
- Signs of virilization (clitoromegaly, masculine body habitus).
  - Girls at any age
- Signs of virilization (penile enlargement, deepening of the voice).
  - Boys <9 years
  - Rapid virilization at any age
- Signs of puberty.
  - Girls (breast development, menarche) <8 years
  - Boys (testicular enlargement) <9 years
- Symptoms of PCOS in girls.
  - Hirsutism
  - Menstrual irregularities
- Metabolic syndrome.
  - Obesity
  - Hypertension
  - Insulin resistance
  - Type 2 diabetes mellitus
  - Dyslipidemia
- The implication of PCOS on future fertility should be discussed with affected young women.
  - At the time fertility is desired, referral to a reproductive endocrinologist is appropriate.

WHEN TO ADMIT

- Hypertension secondary to suspected mineralocorticoid excess
  - Congenital adrenal tumor
  - CAH
  - C-11 hydroxylase deficiency
- CNS symptoms
  - Suspected CNS lesion
  - Headaches
  - Visual changes
- Severe abdominal or pelvic pain
  - Suspected mass
- Marked hyperglycemia requiring insulin treatment

FOLLOW-UP

- If findings are consistent with sexual hair development, without any rapid progression, signs of virilization, or signs of true puberty, close follow-up is recommended.
- Although premature adrenarche has been characterized as a benign condition, studies in girls have shown associations with PCOS, metabolic syndrome, obesity, and acanthosis nigricans.
- Children born small for gestational age are at increased risk for PCOS.
- Offspring of women with PCOS are at higher risk for premature adrenarche.
  - Brothers of women with PCOS have been found to have higher levels of DHEA-S than brothers of unaffected women, suggesting a common cause or risk factor.

COMPLICATIONS

- Adverse effects of OCPs
  - Breast tenderness.
  - Gastrointestinal discomfort.
  - Worsening of headaches in a patient with migraines.
  - The most serious adverse effect is risk for venous thromboembolism.
    - Careful assessment of these risks is warranted.
    - Drospirenone has been implicated in imparting an even higher risk of thromboembolism than other progestins, but it is not clear if that risk is clinically significant.
  - The long-term effect of OCPs on metabolic risks (lipid abnormalities and glucose intolerance) has not been closely studied and should be kept in mind when choosing a regimen.
- Adverse effects of Glucophage
  - Nausea and diarrhea.
    - Can be minimized by titrating a low dose upward and taking with meals.
  - Long-term treatment with Glucophage has been associated with malabsorption of vitamin B_{12}.
  - The most serious, although rare, complication is lactic acidosis.

PROGNOSIS

- Premature adrenarche caused by exogenous sources is reversible with removal of the source.
- Final adult height is usually unaffected if the premature adrenarche is deemed benign (once other causes of premature hair development are excluded).

DEFINITION

- AIDS represents advanced stages of HIV infection and results from progressive immune dysfunction after infection with HIV.
- There are 2 separate HIV viruses.
  - HIV-1 is the predominant virus responsible for disease in the United States and rest of the world.
  - HIV-2 is primarily detected in patients in West Africa; within the United States in individuals from West Africa; or in those who have had sexual contact with individuals from West Africa.

SIGNS AND SYMPTOMS

Diagnosis of HIV/AIDS

- Clinical manifestations range from asymptomatic infection to debilitating disease and death.
- In children, the time from infection to onset of clinical symptoms may be shorter
  - For those who have perinatally acquired infection compared with infection through blood or blood products
  - Than for adults
- Frequently asymptomatic.
  - Infected newborns in the neonatal period.
    - Most with untreated perinatal HIV infection develop symptoms by 2 years of age.
  - Other children may have no or few symptoms for many years.
- Clinical signs and symptoms of untreated or inadequately treated HIV infection or retroviral resistance include
  - Failure to thrive
  - Developmental delay
  - Persistent oral candidiasis
  - Lymphadenopathy
  - Hepatosplenomegaly
  - Chronic diarrhea
  - Recurrent bacterial infections
  - Recurrent herpesvirus infections
- Delayed acquisition of developmental milestones and loss of previously acquired milestones are common.
  - Growth failure is common early in the course of untreated disease.
- Frequent measurements of weight and height are important in
  - Detecting growth disturbances early
  - Monitoring response to interventions

Diagnosing Illness in HIV-infected Children

- Most HIV-infected children with fever and normal clinical examination have self-limited febrile illnesses similar to those of non–HIV-infected children.
  - Fever may indicate a serious infection.
  - Persistent fever can be a diagnostic challenge; identifiable and treatable causes include mycobacterial infection and drug-induced fever.
  - Detailed clinical history and careful physical examination are essential in initial assessment.
  - Close attention should be paid to general appearance and potential areas of focal inflammation, such as
    - Skin
    - Ears
    - Sinuses
    - Lungs
    - Gastrointestinal tract
  - Bacteremia with *Streptococcus pneumoniae* and *Salmonella* can occur in the absence of physical findings.
- Additional diagnostic studies should be obtained on the basis of
  - Age
  - Clinical appearance
  - Degree of immunosuppression
  - Signs and symptoms at the time that the patient seeks care
- Primary HIV infection in adolescents and adults is frequently accompanied by a mononucleosis-like illness characterized by
  - Fever
  - Sore throat
  - Lethargy
  - Lymphadenopathy (seroconversion syndrome)
- See Complications section for more information on secondary and opportunistic infections.

DIAGNOSTIC APPROACH

- The most important factor in identifying HIV-infected women and children is consideration of the diagnosis.
  - Absence of identifiable risk factors does not exclude HIV infection.

LABORATORY FINDINGS

- The number of copies of HIV RNA in plasma can be quantified.
  - Given that HIV is an obligate intracellular parasite, viruses in the plasma represent replicating viruses looking for new host cells.
  - Plasma HIV RNA levels are useful in
    - Predicting the rate of disease progression
    - Modifying antiretroviral therapy
    - Understanding viral dynamics
  - In children with perinatally acquired HIV, HIV RNA levels peak in the first few months of life and decline slowly over several years.
  - Steady-state HIV RNA levels in children are not achieved until 2–6 years of age.
  - HIV RNA levels in adults decrease rapidly to steady-state levels within several months after primary infection.
  - Despite this decrease in HIV RNA level, intense viral replication continues.
- Infection with HIV leads to a progressive decrease in $CD4^+$ T lymphocytes.
  - Qualitative changes in function of $CD4^+$ T lymphocytes occur before the decrease in number.
  - $CD4^+$ T lymphocytes are crucial to B-lymphocyte function; thus, humoral immunity (antibody production) can be significantly impaired in HIV-infected children.
    - Results in poor antibody responses to encapsulated bacteria and immunizations, despite increase in total immunoglobulins (hypergammaglobulinemia)
- Detection of HIV DNA or RNA by polymerase chain reaction (PCR) is the preferred method for diagnosing HIV infection in infants (<18 months).
  - PCR amplifies HIV DNA or RNA sequences and is extremely sensitive in detecting small amounts of virus.
  - Almost all HIV-infected newborns have a positive HIV PCR result by 1 month of age; 40% can be identified in the first 2 days of life.
  - False-positive results are rare with current tests.
    - False-positives may occur because of laboratory contamination.
  - Positive results should be confirmed by PCR testing of a second blood specimen.
  - Early detection of HIV infection allows for initiation of combination antiretroviral therapy in infancy.
    - HIV-exposed neonates should be tested by 48 hours of age.
      - A positive PCR result at 48 hours of age signifies intrauterine infection.
  - If negative, PCR testing should be repeated at 14 days.
    - >90% of infected neonates will have a positive PCR result by 2 weeks of age.
  - Newborns who have negative results for HIV by PCR at 48 hours and at 14 days
    - Should be tested at 4 weeks of age
    - Again at 4–6 months of age if previously negative
  - HIV infection is diagnosed by 2 positive HIV PCR tests performed on separate blood samples.
  - 2 negative PCR results in a non-breastfed infant, the first performed at 1–2 months of age and the second at 4–6 months of age, make the diagnosis of HIV infection extremely unlikely.
  - Negative HIV PCR tests at 2 and 4 weeks of age or 1 negative HIV PCR at 8 weeks of age can be used to provide evidence for presumptive non-HIV infection.
- The HIV enzyme-linked immunosorbent assay (ELISA) detects antibody to HIV and is appropriate for screening children >18 months.
  - HIV ELISA has high sensitivity but lacks specificity.
  - Positive ELISA reactions for HIV are confirmed by Western blot analysis.
    - Western blot detects antibodies to several HIV proteins and is highly specific.
  - False-negative results may occur shortly after primary infection because antibodies to HIV do not achieve detectable levels until 1–3 months after infection.
  - Serologic methods should not be used to confirm HIV infection in children <18 months.
    - Transplacentally derived maternal antibodies result in a positive HIV ELISA with HIV-seropositive mothers, even if the child is not infected.
  - Maternal antibodies can persist for 18 months.
- Laboratory abnormalities often include
  - Anemia
  - Thrombocytopenia
  - Increased immunoglobulin levels

- Laboratory tests to be considered include
  - Complete blood cell count with differential, large-volume blood culture
  - Urinalysis and urine culture
  - Lumbar puncture
- Because HIV antibodies take several months to achieve detectable levels, nucleic acid–based assays (PCR) should be used to diagnose symptomatic primary HIV infection.

IMAGING

- Radiography
  - *Pneumocystis jiroveci* pneumonia (PJP) is most commonly characterized by diffuse alveolar infiltrates.
  - Early in the course of PJP in older children, radiographs may be normal or show minimal changes despite significant cough and even hypoxia.
  - In bilateral lymphoid interstitial pneumonitis (LIP), reticulonodular densities are seen, resembling miliary tuberculosis.
- Computed tomography
  - Characteristic central nervous system (CNS) findings include cerebral atrophy and basal ganglia calcifications.
  - Initial diagnostic studies often include brain imaging.

DIAGNOSTIC PROCEDURES

- HIV-infected children with pulmonary disease who fail to respond to empirical antibiotic therapy, those who are severely ill, and those who are suspected of having PJP should undergo an invasive diagnostic procedure, such as
  - Bronchoscopy with bronchoalveolar lavage
  - Lung biopsy
- Persistent diarrhea.
  - Endoscopy should be considered in refractory cases.
- Initial diagnostic studies of bacterial and viral pathogens may include analysis of cerebrospinal fluid.

CLASSIFICATION

- Centers for Disease Control and Prevention (CDC) immunologic categories based on age-specific $CD4^+$ T-lymphocyte count and percentage of total lymphocytes
  - No evidence of suppression
    - <1 year: ≥1,500/mcL, ≥25%
    - 1–5 years: ≥1,000/mcL, ≥25%
    - 6–12 years: ≥500/mcL, ≥25%
  - Evidence of moderate suppression
    - <1 year: 750–1,499/mcL, 15%–24%
    - 1–5 years: 500–999/mcL, 15%–24%
    - 6–12 years: 200–499/mcL, 15%–24%
  - Severe suppression
    - <1 year: <750/mcL, <15%
    - 1–5 years: <500/mcL, <15%
    - 6–12 years: <200/mcL, <15%
- CDC clinical categories of HIV classification in children
  - N: No signs or symptoms
    - N1: No evidence of suppression
    - N2: Evidence of moderate suppression
    - N3: Severe suppression
  - A: Mild signs or symptoms
    - A1: No evidence of suppression
    - A2: Evidence of moderate suppression
    - A3: Severe suppression
  - B: Moderate signs or symptoms
    - B1: No evidence of suppression
    - B2: Evidence of moderate suppression
    - B3: Severe suppression
  - C: Severe signs or symptoms
    - C1: No evidence of suppression
    - C2: Evidence of moderate suppression
    - C3: Severe suppression

TREATMENT APPROACH

- Administration of antiretroviral therapy can considerably modify disease progression.
- A cure remains elusive.
- Care of HIV-infected children is complex and requires a multidisciplinary team including
  - Pediatricians
  - Experts in antiretroviral therapy
  - Nutritionists
  - Physical therapists
  - Pharmacists
  - Psychologists
  - Social workers
  - Outreach workers
- Effective antiretroviral therapy, with suppression of viral replication and nutritional supplementation, is important to maintaining growth.
  - Supplementation with high-calorie foods or formulas often results in increased body fat rather than lean body weight.
- Effective antiretroviral therapy can minimize or reverse the neurocognitive effects of HIV infection.

- Management of antiretroviral therapy should be directed by a specialist with knowledge of
  - Mechanisms of action of antiretroviral agents
  - Potential toxicities
  - Drug interactions
  - Cross-resistance patterns
- Currently available antiretroviral therapy works by interfering with the functions of the following enzymes:
  - Nucleoside and nonnucleoside reverse transcriptase inhibitors (NNRTIs)
  - Protease inhibitors
  - Entry chemokine receptors or fusion inhibitors
  - Integrase inhibitors
- Most children acquire HIV infection during or near the time of birth, and antiretroviral therapy should be initiated in infancy.
  - Risks of drug toxicity and acquisition of drug-resistant virus are increased.
  - Decisions to initiate early therapy require balancing the benefits and risks.
  - Combination antiretroviral therapy is indicated for all infants in whom HIV infection is diagnosed in the first year of life, regardless of clinical, immunologic, or virologic status.
- For children in whom infection is diagnosed after 12 months of age, the decision to start treatment should be based on
  - Clinical symptoms
  - Plasma HIV RNA level
  - $CD4^+$ T-lymphocyte count
- Combination therapy with reverse transcriptase and protease inhibitors or NNRTIs (highly active antiretroviral therapy) block HIV replication and can result in
  - Dramatic decline in virus production
  - Undetectable plasma HIV RNA levels

SPECIFIC TREATMENTS

Antiretroviral Therapy

- The choice of antiretroviral regimen for children is based on several factors, including
  - Availability of pediatric formulations
  - Potential drug interactions
  - Frequency of drug dosing
  - Potential interactions with other medications
- Before therapy begins, clinical, virologic, immunologic, and nutritional status should be documented.
  - Neuropsychometric testing should be performed in children with suspected neurodevelopmental deficits.
  - Baseline laboratory studies should include
    - Complete blood cell count with differential
    - Liver function tests
    - $CD4^+$ T-lymphocyte count
    - Plasma HIV RNA level
- Combination antiretroviral therapy consists of a protease inhibitor or NNRTI in combination with ≥2 nucleoside reverse transcriptase inhibitors (NRTIs).
  - Protease inhibitors that may be used in children include
    - Lopinavir/ritonavir (preferred)
    - Nelfinavir
    - Ritonavir (alone)
    - Amprenavir
    - Indinavir
    - Fosamprenavir
  - Preferred 2-NRTI backbones include
    - Abacavir plus lamivudine or emtricitabine
    - Didanosine plus lamivudine or emtricitabine
    - Tenofovir plus lamivudine or emtricitabine
    - Zidovudine plus lamivudine or emtricitabine
  - Alternative 2-NRTI backbones include
    - Zidovudine plus abacavir
    - Zidovudine plus didanosine
  - Special circumstances.
    - Stavudine plus lamivudine or emtricitabine could be used as the 2-NRTI backbone.
  - Stavudine plus didanosine should not be used or should be used only with substantial caution because of potential synergistic toxicities.
  - The following antiretroviral regimens or components should *never* be offered as treatment of HIV infection in children:
    - Monotherapy
    - 2 NRTIs alone
    - Tenofovir plus abacavir plus lamivudine or emtricitabine
    - Tenofovir plus didanosine plus lamivudine or emtricitabine
    - Dual NNRTI combinations
    - Combinations of lamivudine plus emtricitabine
    - Combinations of stavudine plus zidovudine)
    - Unboosted saquinavir, darunavir, or tipranavir (These protease inhibitors require boosting with ritonavir because of poor bioavailability.)
  - NNRTIs (nevirapine, delavirdine, and efavirenz) can be used in combination with NRTIs.
    - Nevirapine is preferred in children <3 years.

  - Nevirapine should not be initiated in adolescent girls with $CD4^+$ cell counts of >250 cells/mm^3 or adolescent boys with $CD4^+$ cell counts of >400 cells/mm^3.
  - Efavirenz (only available in capsule form) is preferred in children ≥3 years.
  - Efavirenz should never be given in the first trimester of pregnancy or to sexually active adolescent girls of childbearing potential when reliable contraception cannot be ensured.
- Etravirine, maraviroc, raltegravir, and enfuvirtide (T-20) should not be used in initial treatment regimens for children.
  - In children who have failed other regimens because of antiretroviral resistance, these medications may provide the only options available.
  - They should be used with caution because safety and dosing are not well established for children.
- Protease inhibitors with insufficient data in children to recommend for initial therapy at this time (may be used in adolescents) include
  - Atazanavir
  - Darunavir
  - Tipranavir
  - Saquinavir
- Plasma HIV RNA levels should be measured 4 weeks after the child has started therapy to assess response.

Side Effects

- Common side effects of NRTIs are
  - Anemia and neutropenia with zidovudine
  - Pancreatitis with didanosine
  - Peripheral neuropathy with didanosine and stavudine
  - Influenza-like hypersensitivity reaction with abacavir
    - Rechallenge with abacavir after a hypersensitivity reaction can be fatal.
- Common side effects of the NNRTIs nevirapine, delavirdine, and efavirenz are
  - Rashes
  - Hepatitis
- Side effects of efavirenz include
  - Nightmares
  - Hallucinations
  - Confusion
  - Impaired concentration
- Side effects of protease inhibitors are gastrointestinal symptoms.
- Long-term complications of combination antiretroviral therapy include
  - Lipoatrophy
  - Lipodystrophy
  - Hypercholesterolemia
  - Metabolic syndrome
  - Bone demineralization

Adherence

- Adherence to complex drug regimens is hindered by
  - Large number or volume of medications
  - Poor palatability
  - Varied dosing schedules
  - Different effects of food on drug bioavailability
- Mixing drugs with foods, such as peanut butter or ice cream, may improve adherence in children.
- Behavioral therapy, begun before combination therapy is initiated, can be helpful in
  - Designing a routine medication schedule
  - Teaching parents and caregivers methods to improve adherence
  - Teaching the child techniques for swallowing unsavory medications
- Gastric tubes may be necessary to ensure medication adherence in children because of medication taste or volume problems.
- Strict adherence to the treatment regimen is essential for the prevention of drug resistance.
  - Because of cross-resistance, resistance to one drug can limit effectiveness of other drugs of the same class.
  - Viral sequences obtained from plasma samples can be tested for
    - Drug resistance mutations
    - Susceptibility profiles

Drug Interactions

- HIV protease inhibitors, as well as NNRTIs, are metabolized in the liver by a cytochrome P450 enzyme.
  - Protease inhibitors can inhibit this enzyme and interfere with the metabolism of many other drugs.
  - Protease inhibitors can act as potent inhibitors of 2 other P450 enzymes active in the metabolism of analgesics: β-blockers and phenytoin.
  - Ritonavir can stimulate glucuronidation, thus decreasing concentration of drugs metabolized by this pathway, including sedatives (eg, lorazepam) and the narcotics morphine and codeine.

- Many drugs that have altered metabolism because of protease inhibitors are used in pediatric emergencies, including narcotic analgesics, anticonvulsants, antiarrhythmics, calcium channel blockers, and corticosteroids.
  - These drugs should be used with caution in children receiving protease inhibitors.
  - Drugs that have narrow therapeutic margins require careful monitoring for adverse effects and measurement of drug concentrations.
- Drugs contraindicated for use with protease inhibitors include
  - Meperidine.
  - Midazolam.
  - Astemizole.
  - Terfenadine.
  - Cisapride.
  - Rifampin.
  - Additional medications may be added to this list based on new experience and reports.
- Other medications often prescribed for HIV-infected children are inhibitors of cytochrome P450 enzymes, including
  - Ketoconazole
  - Itraconazole
  - Clarithromycin
  - Erythromycin
- Dose reduction of protease inhibitor may be required because inhibition of cytochrome P450 enzymes by these medications may lead to increase in the plasma concentration of protease inhibitors.
- Inducers of the cytochrome P450 enzyme system are commonly prescribed for HIV-infected children, including
  - Antimycobacterial drugs (rifampin, rifabutin)
  - Anticonvulsants (phenobarbital, phenytoin, carbamazepine)
  - Glucocorticoids (dexamethasone)
- Increased metabolism of protease inhibitors may result in subtherapeutic levels, with the potential emergence of drug resistance.

PJP

- Before widespread prophylaxis for PJP and early antiretroviral therapy, a subset of HIV-infected infants had rapidly progressive disease and died within the first year of life, commonly of PJP.
- Empirical antibiotic therapy depends on the results of clinical assessment and laboratory tests and likelihood of adequate monitoring.
  - A third-generation cephalosporin, such as ceftriaxone or cefotaxime, can be used against gram-positive and gram-negative bacteria.
- PJP should be treated early, usually with co-trimoxazole and corticosteroids.
- Infants <12 months.
  - Neither CD4 cell count nor CD4 percentage is a good predictor of risk.
- Children >12 months.
  - PJP is unusual with normal CD4 cell count or CD4 percentage, moderate immunosuppression, or adherence to appropriate prophylaxis.

Varicella and Herpes Zoster

- HIV-infected children who are susceptible to varicella (no prior natural infection or age-appropriate varicella immunization) should receive
  - Varicella-zoster immunoglobulin preparation within 96 hours of exposure to varicella *or*
  - Intravenous immunoglobulin, if varicella-zoster immunoglobulin is not available
- Disseminated infection can occur with herpes zoster, and oral or parenteral therapy with acyclovir is warranted.

WHEN TO ADMIT

- Ill-appearing children should be hospitalized.

WHEN TO REFER

- HIV-infected children should be managed by physicians who have knowledge and experience in taking care of children with HIV infection.

FOLLOW-UP

- As HIV infection has been managed more effectively with antiretroviral medication combinations, the greatest challenges are
  - Psychosocial issues
  - Adverse effects of medical therapy
- Frequency of medical follow-up visits depends on many factors, including
  - Child's clinical status
  - Expected compliance with therapy
- Follow-up should include measurements of HIV RNA levels and $CD4^+$ T-lymphocyte counts.
- Child care or school attendance.
  - Risk for HIV transmission seems to be negligible, and HIV-infected children should not be restricted from attending child care or school.
    - — Special consideration may be warranted for those with unusual risk factors for transmission, such as frequent biting or scratching, severe dermatitis, or bleeding disorders.

- Supportive care.
  - Many parents and guardians are not willing to tell their child that he or she is infected with HIV.
    - Most children are made aware of their illness through frequent medical visits and medications.
    - The pediatrician's relationship with the patient provides the best position to promote and assist with disclosure.
    - Appropriate disclosure tailored to the child's cognitive level is helpful in alleviating guilt and allowing discussion among the child, caregivers, and health care professionals.
    - Uninfected siblings of HIV-infected children are emotionally affected by the diagnosis and should be included in support groups and counseling.
  - The primary care physician plays a critical role in providing advice and support as the child nears death, helping the family interpret the complexities of critical care and assisting in decisions on the appropriateness of heroic interventions.
    - The pediatrician may be able to assist the family in caring for the dying child at home if critical care is deemed futile.
    - After the child's death, the pediatrician should continue to support the family through the grief process.
    - Because many pediatricians invest much time and emotional energy in caring for an HIV-infected child, many take the opportunity to express sympathy by attending the funeral. This can be an important gesture for the family and the pediatrician.

COMPLICATIONS

- HIV infection and secondary opportunistic infections can involve all organ systems.
- Bacterial and viral pathogens causing meningitis and encephalitis are similar to those in non-immunocompromised children.
  - Common pathogens include
    - *Cryptococcus neoformans*
    - *Toxoplasma gondii*
    - Cytomegalovirus
- Pulmonary disease.
  - PJP
    - Was frequently found before routine prophylaxis of HIV-exposed infants
    - Typically appears at 3–6 months of age
    - Characterized by
      - Tachypnea
      - Cough
      - Hypoxemia
      - Diffuse alveolar infiltrates on chest radiograph
  - Common respiratory pathogens seen in children with HIV and significant respiratory compromise include
    - Respiratory syncytial virus
    - Parainfluenza virus
    - Influenza virus
    - Adenovirus
  - Pneumococcus is the most common bacterial cause of pneumonia in HIV-infected children.
  - LIP is a chronic lung disease resulting from lymphoid hyperplasia in the lungs.
    - Children may be asymptomatic or may have chronic cough and wheezing.
    - Children are typically older than those with PJP.
    - Children with LIP frequently have generalized lymphadenopathy and parotid enlargement.
- Infectious causes of diarrhea in HIV-infected children include pathogens of healthy children and numerous opportunistic pathogens.
  - Common parasitic pathogens causing persistent diarrhea include
    - *Giardia intestinalis*
    - *Entamoeba histolytica*
    - *Cryptosporidium* species
    - *Cystoisospora belli*
  - Cytomegalovirus may cause colitis in advanced immunosuppression.
  - Persistent diarrhea can significantly compromise quality of life and nutritional status.
- CNS disease.
  - Microcephaly
  - Developmental delay
  - Spasticity
  - Abnormal reflexes
  - Gait abnormalities
  - CNS lymphomas (rare)

- Hematologic abnormalities.
  - Leukopenia
  - Anemia
  - Thrombocytopenia (may be the presenting illness)
- Dermatologic conditions include
  - Recurrent herpes simplex
  - Varicella-zoster virus infections
  - Severe molluscum contagiosum
  - Chronic fungal infections
  - Atopic dermatitis
  - Drug-induced eruptions, particularly with co-trimoxazole
- Drug-induced bone marrow suppression can follow therapy with
  - Zidovudine
  - Co-trimoxazole
  - Ganciclovir
- Hepatomegaly and increases in hepatic amino-transferase levels are commonly seen, often in the absence of clinically apparent liver disease.
- HIV cardiomyopathy may lead to congestive heart failure.
- HIV nephropathy is a common cause of proteinuria and can progress to nephrotic syndrome.
- HIV-infected children in whom virus replication is not controlled by antiretroviral therapy are frequently stunted in growth.
  - Severe wasting may be seen in advanced disease.
- Cancers are not as common in HIV-infected children, but lymphomas and leiomyosarcomas can occur.

PROGNOSIS

- High plasma HIV levels and low $CD4^+$ T-lymphocyte counts predict a poor prognosis.

PREVENTION

Preventing Perinatal HIV Transmission

- Prevention of maternal-neonate HIV transmission.
  - Identification of HIV-infected women before or during pregnancy is critical.
  - Prenatal HIV counseling and testing should be provided to all pregnant women.
  - Initial HIV antibody testing should be performed early in pregnancy and repeated in the third trimester for women at risk.
- Antiretroviral therapy administered during pregnancy and delivery and to newborns and infants during the first 6 weeks of life greatly reduces the rate of perinatal HIV transmission.
  - HIV-infected pregnant women should receive the optimal medical and antiretroviral therapy required for their own health.
  - If deferral of antiretroviral therapy is acceptable because of normal immune status, antiretroviral therapy is still indicated during pregnancy to optimally suppress the HIV viral load and prevent maternal-neonate HIV transmission.
- Although the total number of perinatal infections has decreased, the proportion caused by intrauterine transmission has increased.
  - This supports a greater role for antiretroviral therapy and mode of delivery on influencing intrapartum transmission.
- Administration of zidovudine to women during pregnancy and labor and to newborns and infants for the first 6 weeks of life has been shown to reduce perinatal HIV transmission by two-thirds (from 26% to 8%).
  - This regimen was previously the standard of care for HIV-infected pregnant women and their newborns.
- Early identification of HIV-infected pregnant women allows for
  - Appropriate care of the mother
  - Avoidance of ongoing HIV exposure of the neonate through human milk
  - Early institution of PJP prophylaxis for the neonate/infant at 4–6 weeks of age
- Cesarean delivery reduces the risk for perinatal HIV transmission.
  - Should be strongly encouraged for women with viral loads consistently >1,000 copies/mL.
  - If viral load is <1,000 copies/mL, the benefits may not outweigh the risks.

Immunization

- The Infectious Diseases Society of America is developing guidelines that should assist physicians determining optimal primary series and booster dosing of vaccines for HIV-infected children.
  - Immunizations are generally safe for HIV-infected children.
  - Immune suppression caused by HIV results in less assurance of protection after immunization than in HIV-uninfected children.
  - The small risk for serious complications from live viral vaccines has led to special recommendations for HIV-infected children.

- Live oral rotavirus vaccine should not be administered to severely immunocompromised children.
  - HIV-exposed infants with testing that does not support HIV infection may receive an initial dose of live oral rotavirus vaccine before documentation that the infant is not infected (negative PCR after 4 months of age).
- Toxoids, subunit vaccines, inactivated vaccines, and recombinant vaccines are not associated with increased risks of complications in HIV-infected children, including
  - Diphtheria and tetanus toxoids.
  - Acellular pertussis vaccines.
  - Inactivated poliovirus vaccine.
  - *Haemophilus influenzae* type b.
  - Meningococcal and pneumococcal conjugate vaccines.
  - Inactivated influenza vaccine.
  - Hepatitis A and B vaccines.
  - Human papillomavirus vaccine should be given to HIV-infected females and males at 11–12 years of age with catch-up to age 26 years.
- These vaccines should be administered to HIV-infected children according to routine immunization schedule.
  - Because of increased risk for invasive infection with *S pneumoniae,* immunization of HIV-infected children with pneumococcal conjugate vaccine is particularly important.
  - HIV-infected children may develop lower antibody titers than healthy children after immunization and are more likely to lose protective antibody earlier.
- Live-virus vaccines may result in infection and disease resulting from vaccine virus in severely immunocompromised HIV-infected children, although the risk is quite small. Examples include
  - Varicella vaccine
  - Measles, mumps, and rubella (MMR) vaccines
- After a single reported death, advisory groups in the United States recommended withholding measles vaccine from HIV-infected children with severe immunosuppression, defined as $CD4^+$ T-lymphocyte count <15%.
  - MMR vaccine should be administered to HIV-infected children at 12 months and a second dose 1 month (minimum of 28 days) later, unless severely immunocompromised ($CD4^+$ <15%).
  - Immune response to measles vaccine in HIV-infected children may be poor, and vaccinated children may remain susceptible despite prior immunization.
  - Serious complications after mumps or rubella immunization have not been reported.
  - The combination vaccine MMR plus varicella (MMRV) should not be given to HIV-infected children.
- Live varicella virus vaccine is also recommended for HIV-infected children on the basis of their degree of immunosuppression and symptoms.
  - The American Academy of Pediatrics Committee on Infectious Diseases recommends varicella vaccine at 12 months of age and a second dose 3 months later for asymptomatic and mildly symptomatic HIV-infected children who have $CD4^+$ T-lymphocyte percentages ≥15%.
  - Serious adverse events after administration of varicella vaccine to HIV-infected children are rare.

Antimicrobial Prophylaxis

- PJP prophylaxis should be administered to HIV-exposed infants beginning at 6 weeks of age if HIV status is not established.
  - PJP prophylaxis does not need to be started for infants who are presumptively negative.
  - Continue until 12 months of age or until HIV has been excluded.
  - Criteria for discontinuing PJP prophylaxis are age related.
    - Evidence of immune reconstitution ≥3 months on effective antiretroviral therapy
- PJP prophylaxis is administered
  - For children 1–5 years of age if $CD4^+$ T-lymphocyte count is <500 cells/mm^3
  - For children 6–12 years of age if $CD4^+$ T-lymphocyte count is <200 cells/mm^3
- Lifelong PJP prophylaxis is recommended for children who have a history of PJP, despite immune reconstitution.
- Recommended regimen is co-trimoxazole taken orally 3 days a week.
- Alternative regimens include dapsone or pentamidine.
- HIV-infected children who have recurrent oral candidiasis may benefit from antifungal prophylaxis.
  - Oral nystatin
  - Clotrimazole
  - Fluconazole

- Oral azithromycin weekly or clarithromycin daily for prophylaxis against *Mycobacterium avium-intracellulare* infection is indicated in children based on age-related $CD4^+$ cell counts.
  - >6 years with $CD4^+$ cell counts <50 cells/mm^3.
  - 2–5 years with $CD4^+$ cell counts <75 cells/mm^3.
  - 1–2 years with $CD4^+$ cell counts <500 cells/mm^3.
  - Infants <1 year with $CD4^+$ cell counts <750 cells/mm^3.
- Immunoglobulin should be provided to susceptible (no age-appropriate measles immunization) HIV-infected children within 6 days of exposure to measles.
  - Measles immunization should be delayed 6 months after receipt of immunoglobulin.

Postexposure Prophylaxis After Community Needlestick Injuries

- Parents, caregivers, and physicians often are most concerned about transmission of HIV after accidental injury from a discarded needle.
- No consensus or recommendation is available to guide management in such circumstances.
- Risk for HIV transmission after occupational exposure to HIV-infected blood is 0.3%.
- Most experts agree that risk after community needlestick injury is lower than risk after occupational exposure.
- Factors to be considered in the use of antiretroviral agents for postexposure prophylaxis include
  - Potential risk for HIV transmission
  - Drug toxicities
  - Ability and willingness of the family to adhere to therapy
- Regimens for occupational postexposure prophylaxis may be followed.
- Pediatricians caring for adolescents must ensure that their patients have knowledge of the risks for acquiring HIV and other sexually transmitted infections through unprotected sex and be counseled on safe-sex practices.

DEFINITION

- Hoarseness is a symptom of vocal dysfunction that describes a breathy, harsh, coarse, strained, or raspy voice.
- In children, "hoarseness" can be used to describe the quality of voice and quality of cry.
- Although sometimes occurring concurrently, hoarseness should be discerned from stridor, a sign of turbulent airflow caused by obstructive lesions in the airway.
- Causes vary by age group and can be attributed to infectious, anatomic, traumatic, inflammatory, neoplastic, neurologic, and iatrogenic sources.

HISTORY

- A thorough history is essential.
- Age is a critical factor in the development of an appropriate differential diagnosis.
  - Neurologic and congenital fixed anatomic lesions typically occur at birth.
  - Inflammatory, neoplastic, traumatic, or iatrogenic causes occur later.
- Information on quality of the voice with speech or crying, exacerbating or alleviating factors, and associated symptoms.
- The onset and course of dysphonia should be considered.
  - Intermittent dysphonia may be related to infectious or inflammatory causes, such as laryngitis.
  - Persistent dysphonia may suggest a fixed anatomic lesion.
  - Progressive, unremitting hoarseness may suggest an enlarging neoplasm.
- A review of medical and surgical history is helpful.
- Underlying reflux may be present in patients with such symptoms as
  - Regurgitation or vomiting
  - Feeding difficulties
  - Throat clearing
  - Foreign body sensation
  - Cough
- Stridor that accompanies hoarseness should be investigated and treated in an expeditious fashion.
  - Turbulent airflow resulting from airway obstruction may be life threatening.

PHYSICAL EXAMINATION

- Thorough physical examination should include a complete head and neck examination with inspection of cranial nerve function for craniofacial anomalies.
  - Cutaneous head and neck hemangiomas may suggest a potential laryngeal hemangioma.
  - Signs of aspiration during deglutition may be suggestive of sensorimotor causes of dysphonia, such as vocal cord paralysis.

DIFFERENTIAL DIAGNOSIS

- Forming a differential diagnosis for the hoarse child depends on
  - Quality of hoarseness
  - Progression of symptoms
  - Related infection
  - History of surgery or trauma
  - Associated respiratory distress

Causes, by Patient Age[1]

- The age of the patient at the onset of hoarseness is a useful way to organize potential causes.
  - 0–6 months
    - Traumatic: intubation
    - Iatrogenic: surgical
    - Neurogenic: central or peripheral
    - Neoplastic: hemangioma
    - Congenital: web, cleft, cyst
  - 6 months–5 years
    - Traumatic: foreign bodies, intubation
    - Infection: upper respiratory infection (URI)
    - Neoplastic: papillomas
    - Behavioral, traumatic: nodules
    - Inflammatory: allergy, laryngopharyngeal reflux (LPR)
  - 5–13 years
    - Behavioral, traumatic: nodules
    - Infectious: URI
    - Inflammatory: allergy, LPR
    - Neoplastic
  - 13–18 years
    - Infectious: URI
    - Inflammatory: allergy, LPR
    - Behavioral, traumatic
      - Male: mutational or transitional voice
      - Female: nodules
    - Functional: muscle tension dysphonia

Neonate and Infant

- Hoarseness at birth or shortly thereafter is most often attributable to causes that are
  - Congenital
  - Traumatic or iatrogenic
  - Neoplastic
  - Inflammatory
- In this age group, "hoarseness" often refers to a weak or breathy cry.
- Neonatal vocal cord paralysis is a well-known cause of hoarseness and stridor.
  - Bilateral vocal cord paralysis is usually congenital and frequently causes respiratory distress and stridor.
    - Central nervous system (CNS) disease (eg, Arnold-Chiari malformation) must be ruled out.
  - Unilateral vocal cord paralysis is more likely to exhibit initially as hoarseness or dysphagia.
  - A weak or breathy cry after thoracic or cervical surgery may indicate recurrent laryngeal nerve injury as a source of iatrogenic vocal cord paralysis.
  - Traumatic intubation can cause arytenoid cartilage dislocation, with subsequent vocal cord immobility and hoarseness.
- Congenital laryngeal webs result from failure of larynx to canalize fully during embryologic development.
  - Webs may occur exclusively with hoarseness, but they may be associated with aphonia, stridor, and respiratory distress.
  - Webs vary from thin slips of tissue between the anterior areas of the vocal cords to complete laryngeal atresia (congenital high airway obstruction syndrome).
- Laryngeal saccular cysts are characterized by symptoms of airway obstruction and dysphagia.
  - Saccular cysts are filled with mucinous fluid and arise as a result of an abnormal dilation of the saccule of the larynx secondary to secretory outflow obstruction.
- Posterior laryngeal clefts are an uncommon anomaly resulting in an abnormal opening in the posterior larynx.
  - Clefts can involve the posterior laryngeal commissure or may extend through the cricoid inferiorly through the tracheoesophageal septum.
  - Symptoms depend on extent of the cleft and, at birth, typically include aspiration, stridor, respiratory distress, and weak cry.
- Subglottic hemangiomas classically occur at 1–6 months of age, with varying degrees of respiratory distress, stridor, cough, dysphagia, and hoarseness.
  - Natural history of hemangiomas is that of proliferation followed by involution.
  - Subglottic hemangiomas can be unilateral, bilateral, or circumferential.
  - More common in girls than in boys.
  - Cutaneous hemangiomas of the head and neck are found concurrently in ~50%.
- The association among gastroesophageal reflux (GER), LPR, and neonatal laryngeal disorders (eg, hoarseness, posterior laryngitis, silent aspiration) remains complicated and controversial (see Dysphagia and Gastroesophageal Reflux Disease).
  - GER refers to the backflow of stomach contents into the esophagus.
  - LPR refers to the backflow of stomach contents into the laryngopharynx.

Older Children

- Subject to many of the same sources of hoarseness as adults.
- Leading causes include infectious, inflammatory, traumatic, and neoplastic conditions, such as laryngitis, LPR, vocal nodules, and respiratory papillomata.
- Infectious disorders, such as infective laryngitis, supraglottitis, and laryngotracheobronchitis, rarely present a diagnostic challenge.
- Concern over the airway should always take precedence; a hoarse voice may be an early indicator of impending airway compromise by epiglottitis.
- The role of LPR in children is debated; however, infrequent reflux events have been shown to cause hoarseness in adults.
  - LPR has been found in association with pediatric conditions, such as vocal fold nodules, posterior laryngitis, false vocal cord edema, vocal cord granulomas, functional voice disorders, and hoarseness.
  - Animal studies have shown that subglottic stenosis results when gastric acid is applied to the subglottic mucosa of dogs.
- Vocal nodules arise from phonotrauma or voice abuse more frequently in boys than in girls.
  - Symptoms may fluctuate on the basis of aggravation by vocal abuse and respiratory tract infections.

- Symptoms may worsen suddenly when polyps swell from internal hemorrhage from vocal trauma.
- Children with vocal nodules may share symptoms with other family members with similar traits.

- Airway trauma is a potential cause of hoarseness.
  - Sources include blunt or penetrating injuries and intubation trauma.
- Progressive and unrelenting hoarseness suggests a possible neoplastic cause.
  - 98% of pediatric laryngeal neoplasms are benign; recurrent respiratory papillomatosis (RRP) is by far the most common lesion.
  - RRP may be found on other upper aerodigestive tract mucosal surfaces and have a characteristic "cluster of grapes" appearance.
  - RRP may be indistinguishable from the rare laryngeal squamous cell carcinoma of childhood.

Adolescents

- Hoarseness may be of behavioral or psychogenic etiology.
- Mutational voice disorder occurs in male adolescents, resulting in hoarseness and high pitch during the stress of physiologic pubertal voice change.
- Paradoxical vocal fold dysfunction (seen more frequently in girls) is psychogenic in origin and often misdiagnosed as asthma.

IMAGING

- Diagnostic imaging is of prime importance when CNS disease, external compression, malignancy, or external trauma is suspected.
- Chest and neck plain-film radiography may demonstrate mediastinal masses, cardiovascular anomalies, or abnormalities in the air column suggesting possible infectious or obstructive diseases.
- Computed tomography (CT) and virtual bronchoscopy are excellent methods for
  - Specifically defining the caliber of the airway.
  - Delineating the site and extent of pathologic changes in airway caliber.
  - Indications for laryngeal or neck CT include congenital cysts, solid neoplasms, and external trauma.
- Magnetic resonance imaging is helpful
  - When CNS disease is suspected
  - In evaluating possible airway hemangiomas
  - In identifying vascular malformations
- Barium esophagography has variable sensitivity and specificity for the diagnosis of LPR.
  - Useful mainly for detecting anatomic abnormalities, such as hiatal hernia

DIAGNOSTIC PROCEDURES

Laryngoscopy

- Indirect mirror laryngoscopy, flexible nasopharyngolaryngoscopy, and rigid videostroboscopy are all methods for visualizing the larynx that can provide useful clues.
- Indirect laryngoscopy using a mirror
  - Can be performed on cooperative children.
  - Can visualize gross disease and inflammatory changes in the larynx.
  - This technique has largely been replaced.
- Flexible fiber-optic nasopharyngolaryngoscopy
  - Provides clear views of laryngeal anatomy and function.
  - Can be performed on virtually all age groups, although toddlers and patients who are developmentally delayed pose the greatest challenge.
  - Topical anesthesia and topical decongestants can facilitate examination.
  - Examination in a non-monitored setting is not advisable if the patient has a tenuous airway or severe congenital cardiac anomalies.
- Videostroboscopy.
  - A rigid, angled telescope placed gently into the oropharynx is used for dynamic examination of laryngeal anatomy and function.
  - The examination requires a cooperative child.
  - Uses rapidly pulsed light to examine vibratory characteristics of the vocal fold mucosa.
  - Recorded on video to allow repeated assessments viewed at different speeds to enhance visualization of the vibratory quality of the laryngeal mucosa.
  - Vocal nodules or other lesions on surface of the vocal fold will dampen the mucosal wave.

Reflux Testing

- In the absence of identifiable disease in the hoarse child, investigation into LPR may be warranted.
- Several diagnostic modalities exist for the workup of LPR, including
  - pH monitoring
  - Impedance testing
  - Nuclear medicine scintiscan
  - Barium esophagoscopy (See Imaging section.)
  - Direct laryngoscopy with or without biopsy

- Ambulatory 24-hour single-electrode pH monitoring is the gold standard for the diagnosis of GER.
- However, double-electrode pH probe, with distal esophageal and pharyngeal electrodes, is thought to be the best method for diagnosing LPR and the otolaryngological manifestations of GER.
- Although pH-monitoring studies remain the gold standard for diagnosis of GER and LPR, they do not detect episodes of nonacidic reflux.
- Multichannel intraluminal impedance monitoring and nuclear medicine scintigraphy.
  - Measure acidic and nonacidic episodes of reflux, which may play a role in apnea, apparent life-threatening events, aspiration, and sleep disturbance.
  - Nuclear medicine scintiscans have specificity of 83%–100% but have been shown to be only 15%–59% sensitive and lack a standardized technique, making comparisons between studies of limited use.
  - Impedance monitoring evaluates the pH-independent change in intraluminal electrical resistance that occurs with the movement (anterograde or retrograde) of a bolus of food, liquid, or gas within the esophagus.
    - This technique may be a reliable tool for evaluating the association between GER-related symptoms and nonacidic reflux events.
    - It may ultimately replace pH monitoring as the standard tool for detecting LPR in infants and children.
- Laryngoscopy with biopsy.
  - May be the most specific test for LPR.
  - At least one study has failed to show a correlation between laryngoscopy and upper pH probe findings with significant laryngeal histopathologic inflammatory findings.

TREATMENT APPROACH

- Most pediatric hoarseness results from benign, reversible, and self-limited disease.
- Some causes of hoarseness are progressive, malignant, and potentially life threatening.
- Thorough evaluation, precise diagnosis, and appropriate intervention are, therefore, essential.

SPECIFIC TREATMENT

Congenital Lesions

- Management of hoarse voice resulting from unilateral or bilateral vocal cord paralysis is usually secondary to stabilization of the airway and management of dysphagia and aspiration.
- Tracheotomy is sometimes required in patients with bilateral vocal cord paralysis.
- Conservative management has been advocated in selected patients.
  - Patients with congenital or acquired unilateral vocal cord paralysis frequently experience spontaneous resolution of paralysis or compensatory movement of the unaffected cord over time.
  - Recovery has been noted up to 11 years after paralysis.
- In cases of persistent unilateral cord paralysis with persistent hoarseness, the treatment of choice remains speech therapy.
  - Successful surgical vocal cord medialization techniques have been reported.
- Laryngeal webs are managed surgically, endoscopically, or via more extensive open laryngotracheal reconstruction techniques.
  - The type of operation depends primarily on location and extent of the lesion.
  - Thin webs are more amenable to endoscopic management.
- Saccular cysts of the larynx.
  - Often managed endoscopically via aspiration and marsupialization using sharp dissection or with a carbon dioxide (CO_2) laser.
  - Cyst recurrence is well documented following endoscopic management.
  - Open resection of the cyst may be necessary.
- Posterior laryngeal clefts vary greatly in extent and symptoms.
  - Extensive or symptomatic clefts must be repaired as early as possible.
  - Endoscopic repair is possible in small clefts limited to the larynx and upper trachea.
  - More extensive open techniques are used for larger clefts.
  - Tracheotomy may be placed in cases in which staged reconstruction is necessary.
  - A gastrostomy tube is often necessary to limit aspiration and protect the operative site.

Neoplasia

- Subglottic hemangioma is a complicated airway anomaly without universally accepted treatment.
  - Numerous management options exist, including
    - Close observation
    - Systemic or intralesional steroids
    - Laser ablation
    - Open surgical excision
    - Tracheotomy
- RRP is an airway tumor with a large number of accepted primary and adjuvant therapeutic modalities.
  - CO_2 laser excision remains a popular method for removing laryngeal papilloma, although it is associated with potentially severe sequelae, such as
    - Airway fire
    - Scarring
    - Chronic laryngeal edema with airway compromise
    - Vocal fold scarring
    - Poor voice
  - Nonlaser therapies, such as cold dissection and powered debridement, have been used successfully for excision of RRP.
  - Pulsed dye laser therapy was introduced as a less traumatic alternative that can be used safely and effectively under local anesthesia in older patients.
  - Nonlaser therapies, such as cold dissection and powered débridement, have also been used successfully for excision of RRP.
  - Adjuvant therapies have been used with varying degrees of efficacy and safety, such as
    - Intralesional cidofovir
    - Interferon alfa
    - Indole-3-carbinol
    - Heat-shock protein E7

Inflammation and Infection

- Acceptable for the management of GER and LPR in infants and children.
  - Behavioral and lifestyle modifications
  - Pharmacotherapy using
    - Histamine-2 antagonists
    - Proton-pump inhibitors
    - Prokinetic agents
    - Antacids
  - Surgical therapy with fundoplication
- Viral laryngitis and laryngotracheobronchitis are generally treated conservatively.
  - May require airway protection or intravenous (IV) steroids in severe cases
- Bacterial infections, such as epiglottitis and membranous laryngotracheobronchitis, necessitate
  - Early airway protection
  - IV antibiotics directed against *Staphylococcus aureus* and *Haemophilus influenzae,* unless culture results direct differently

Trauma

- Management of vocal fold nodules resulting from phonotrauma.
  - Behavioral modification.
  - Speech therapy aimed at maximizing vocal hygiene.
  - Surgical excision, rarely, because failure to correct underlying voice misuse is likely to result in recurrence.
- Arytenoid dislocation resulting from intubation trauma can be adequately treated if recognized and reduced early under anesthesia with microlaryngoscopy.
- Blunt laryngeal trauma.
  - Close observation.
  - Possibly systemic corticosteroids.
  - Tracheotomy in cases of severe laryngeal injury and edema.
  - In adolescents with laryngeal fracture, open reduction and fixation may be required.

WHEN TO REFER

- Recognized cardiac, esophageal, or neurologic disease
- Progressive hoarseness
- Presence of cutaneous hemangioma
- Hoarseness after external trauma or uneventful intubation
- Poor speech intelligibility or psychosocial sequelae
- Hoarseness that has been present since birth

WHEN TO ADMIT

- Presence of respiratory distress, stridor, tachypnea, or tachycardia
- Hoarseness following external trauma

REFERENCE

1. Adapted and modified with permission from Smith ME, Gray SD. Voice. In: Bluestone CD, Stool SE, Kenna MA, eds. *Pediatric Otolaryngology.* 4th ed. Philadelphia, PA: WB Saunders; 2003

Human Herpesvirus 6 and Human Herpesvirus 7 Infections

DEFINITION

- Human herpesviruses 6 (HHV-6) and 7 (HHV-7) are ubiquitous, lymphotropic, herpesviruses.
- In otherwise healthy children, the spectrum of diseases associated with HHV-6 and HHV-7 is far broader than the benign illness of roseola.
- Commonly reactivated in the immunocompromised host and potentially associated with severe disease.
- Roseola infantum.
  - Also known as exanthem subitum, 3-day fever, sixth disease, and pseudo-rubella.
  - A self-limited, acute illness characterized by fever for 3 days followed by a rash.
  - First described in the early 1900s, but HHV-6 and HHV-7 were discovered in 1986 and 1990, respectively.

SIGNS AND SYMPTOMS

- Recognition of the illness is based almost entirely on the observation of a classic clinical course.

Nonspecific Viral Illness

- Abrupt onset of high fever is characteristic; body temperature 39.0°C–40.0°C (102.2°F–104.0°F) or higher, typically lasting 5–7 days.
- Additional symptoms may include fussiness, nonspecific upper respiratory symptoms such as cough or rhinorrhea, inflamed tympanic membranes, rash, vomiting, and diarrhea.
- HHV-6 infection: Children have significantly higher temperatures, appear sicker, and are more irritable than age-matched children with acute febrile illnesses attributed to other causes.
- Presenting symptoms for HHV-6 and HHV-7 are in **Table 1.**

Roseola

- Fever resolves dramatically while an erythematous maculopapular rash simultaneously appears initially on the face, neck, or trunk and then spreads to extremities.
  - It is usually not painful and does not itch.
  - Macules/papules do not blanch or blister and may be surrounded by a light halo.
  - Rash fades within hours to 2 days; with defervescence, child seems to have recovered, despite the rash.
- The disease may be accompanied by
  - Painless posterior auricular, suboccipital, or cervical lymphadenopathy
  - Slight eyelid edema
  - Nagayama spots, which are erythematous macules appearing on the soft palate and base of the uvula
- Less common features include cough, rhinorrhea, or bulging fontanel (in one-quarter of patients).

Central Nervous System (CNS) Manifestations

- Seizures.
  - HHV-6 and HHV-7 have been associated with febrile seizures and status epilepticus in children.
  - It is unclear how HHV-6 and HHV-7 contribute to the pathogenesis of febrile seizures.
  - Some evidence suggests that HHV-6B may play a role in certain types of epilepsy.
- HHV-6 infection.
  - Primary HHV-6 infection is found in 10%–40% of children with febrile seizures within the first 2 years of life and in one-third of patients with febrile status epilepticus.
  - Appears to be associated with more severe, atypical, prolonged, and recurrent seizures.
- HHV-7.
  - Febrile seizures appear more common in children with HHV-7 infections compared with those infected with HHV-6.
- Infections with these viruses may simply serve as common febrile illnesses during the age of highest susceptibility.
- One small study of children with a first or second febrile seizure showed that the incidence of primary HHV-6 infection was comparable to that in febrile age-matched children without seizures.
- Other neurological manifestations.
  - Occasional cases of meningitis and severe encephalitis attributable to HHV-6 and HHV-7 infections have been reported, often associated with long-term sequelae.
- HHV-6.
  - Implicated in cases of progressive multifocal leukoencephalopathy, multiple sclerosis, and other neurologic diseases.
  - Found in brain tissue of some patients by immunohistochemical staining.

Table 1. Relative Frequency of Presenting Symptoms In Children With Primary Human Herpesvirus 6 and Human Herpesvirus 7 Infections

	HHV-6	HHV-7
Median age (months)	8	26
Fever	++++	++++
Irritability	+++	++++
Upper respiratory symptoms	++/+++	+
Rash	++	+
Vomiting/diarrhea	++	++
Seizures	+	+++

Abbreviations: HHV-6, human herpesvirus 6; HHV-7, human herpesvirus 7.

Key: + = ~0%–25%; ++ = ~26%–50%; +++ = ~51%–75%; ++++ = ~76%–100%.

Data derived from Hall CB, Long CE, Schnabel KC, et al. Human herpesvirus-6 infection in children. A prospective study of complications and reactivation. *N Engl J Med*. 1994;331(7):432–438; Caserta MT, Hall CB, Schnabel K, Long CE, D'Heron N. Primary human herpesvirus 7 infection: a comparison of human herpesvirus 7 and human herpesvirus 6 infections in children. *J Pediatr*. 1998;133(3):386–389; Zerr DM, Meier AS, Selke SS, et al. A population-based study of primary human herpesvirus 6 infection. *N Engl J Med*. 2005;352(8):768–776; and Hall CB, Caserta MT, Schnabel KC, et al. Characteristics and acquisition of human herpesvirus (HHV) 7 infections in relation to infection with HHV-6. *J Infect Dis*. 2006;193(8):1063–1069.

- Causation has not been established, and further research is needed.
- Associated cerebrospinal fluid (CSF) abnormalities are infrequent and similar to those found in other infectious causes of meningitis or encephalitis.

- Diagnosis of HHV-6 or HHV-7 as causative agents of CNS disease is often made by identification of viral DNA in the CSF.
  - Because these viruses may establish latency, HHV-6 or HHV-7 DNA has been detected in the CSF of children with infection (with and without seizures) and without infection.

Other Manifestations in Immunocompetent Hosts

- A number of case reports implicate HHV-6 as a cause of chronic and acute hepatitis, ranging from mild to fulminant disease.
  - Although some case reports have relied on seroconversion to define the causative role of HHV-6, others have identified HHV-6 DNA in liver biopsy specimens.
  - The differential diagnosis for mononucleosis-like illnesses in adults should include HHV-6, which accounts for ~9% of cases.
- HHV-6 and HHV-7 have been isolated from patients with many other conditions.
  - Pityriasis rosea, lichen planus
  - Gianotti-Crosti syndrome
  - Several other dermatologic diseases
  - Drug reaction with eosinophilia and systemic symptoms
  - Stevens-Johnson syndrome
  - Immune thrombocytopenia purpura
  - Aplastic anemia
  - Myocarditis
  - Hemophagocytic lymphohistiocytosis
- Because viral reactivation may occur during acute illnesses, causality is difficult to ascertain.
- The role of HHV-7 in other diseases is even less clear than its association with roseola.

Congenital Infection

- Appears to be uncommon.
  - In a large prospective study, congenital HHV-6 infection, defined as viral DNA in cord blood, occurred in 1% of neonates.
  - No distinct features or clinical abnormalities in the neonate.
  - No cases of congenital HHV-7 infection have been reported.
- Intrauterine transmission of HHV-6 may occur by transplacental infection or chromosomal integration in germ cells.
- HHV-6 has the ability to integrate its genome into human chromosomes and can be inherited from one or both parents.
- It is not known whether clinical manifestations or long-term sequelae may subsequently develop.

- A recent study involving 57 infants with congenital HHV-6 infection demonstrated possible detrimental effects on neurodevelopment at 12 months of age compared with controls without infection.

Infection in Immunocompromised Patients

- Syndrome associated with fever, rash, encephalitis, pneumonitis, hepatitis, delayed engraftment, leukopenia, and thrombocytopenia in children following bone marrow transplants.
- Limbic encephalitis (insomnia, short-term memory loss, hallucinations, and magnetic resonance imaging [MRI] abnormalities in the amygdala and hippocampus) is well documented.
- HHV-6.
  - May reactivate during periods of immunosuppression.
  - Implicated in graft-versus-host disease.
    - Following solid-organ transplantation (SOT), overt clinical disease associated with HHV-6 occurs in <1% of patients.
    - Immunomodulatory effects of infection likely play a role in other associated diseases.
  - Associated with higher rates of rejection and invasive fungal infections.
  - Co-detection with cytomegalovirus (CMV) may indicate increased risk for severe CMV.
- HHV-7.
  - Disease caused by reactivation is not well characterized.
  - Reported in cases of encephalitis and myelitis following hematopoietic stem cell transplant (HSCT).
  - Immunomodulatory effects may predispose transplant recipients to opportunistic infections or severe CMV disease.
    - Clinical findings have been less frequently reported than with HHV-6 reactivation.
- The role of HHV-6 or HHV-7 in HIV infection is inconclusive.
  - HHV-6 infection does not seem to affect the progression of HIV to AIDS.

DIFFERENTIAL DIAGNOSIS

- HHV-6 and HHV-7 infections are difficult to differentiate acute from past, reactivated infection.
  - Confounded by intrinsic characteristics of herpesviruses
  - Except for roseola, which is the only manifestation that is easily recognized clinically
- Roseola is often confused with other exanthematous diseases.
  - Rubella
    - Concurrent rash and fever
    - Enlarged, often tender, lymph nodes
- Rubeola
    - Distinguished by coryza, respiratory symptoms, and Koplik spots.
- Enterovirus exanthems
  - Usually occur in epidemics.
  - Involve older and younger children.
  - Are more common in the late summer and fall.
- Parvovirus B19 causes erythema infectiosum, or fifth disease.
  - Affects the school-aged child
  - Initial classic slapped-cheek appearance
- Scarlet fever.
  - More confluent rash
  - Associated with marked pharyngitis
- Drug eruptions (especially from sulfa-containing preparations).
  - Not regularly preceded by fever
  - Tend to be diffuse
- Kawasaki disease.
  - Accompanied by more prolonged fever and concurrent rash
  - Bilateral conjunctival injections

DIAGNOSTIC APPROACH

- Presence of virus may be irrelevant to the disease or condition being investigated, and signs and symptoms are nonspecific.
- Except in certain situations, there is no clinical need to confirm infection with HHV-6 or HHV-7 serologically or virologically.
  - Identification in febrile infants does not obviate the need to evaluate for serious bacterial infection.
  - ~10% of young infants have concurrent viral and bacterial infections, usually bacteriuria.
- Because roseola is an inconsequential illness, confirmation of the diagnosis is rarely needed.
- Confirmation in children with complex neurologic syndromes may help rule out vaccine administration as the cause.
- Newly developed diagnostic methods to differentiate latent from actively replicating virus may eventually help in diagnosis and pathogenesis.

LABORATORY FINDINGS

- During acute HHV-6 infection, white blood cell, absolute lymphocyte, and neutrophil counts are decreased compared with other febrile illnesses.
- In some cases, relative thrombocytopenia is observed.
- Results of other routine laboratory tests are typically normal.
- Multiple assays for detecting HHV-6 and HHV-7 infection have been developed, including serologic tests, isolation of virus by tissue culture, and detection of viral DNA or RNA by polymerase chain reaction.
  - Diagnosis based only on seroconversion, rise in antibody titers, or viral isolation can be misleading.
  - Increases in immunoglobulin G (IgG) and IgM titers may represent viral reactivation rather than new infection.
  - Blood viral DNA may be detected with both primary and latent infections.
    - Detection of DNA in other body fluids and tissues does not differentiate new infection from past infection.
- A combination of serology (acute and convalescent) and direct viral identification is recommended if clinically indicated.
  - Serologic tests include immunofluorescent antibody, neutralization, and enzyme immunoassays.
    - Do not differentiate between HHV-6A and HHV-6B and may cross-react with HHV-7.
    - Detection of low-avidity (≤6 weeks of infection) and high-avidity (>6 weeks) HHV-6 and HHV-7 antibodies may help confirm recent primary infection.
    - Seroconversion from negative to positive in paired sera provides evidence for recent primary infection.
  - HHV-6 and HHV-7 DNA can be detected in blood and CSF in reference laboratories.
    - Viral DNA detection does not necessarily differentiate acute from past infection.
    - Not specific enough to differentiate chromosomally integrated HHV-6 infection.
    - Chromosomally integrated HHV-6 is suspected based on the presence of consistently high viral HHV-6 loads in blood and is confirmed by detection of HHV-6 DNA in hair follicles.
- In cases of invasive disease, histopathology and immunohistochemical stains from biopsy specimens may be helpful.

IMAGING

- Brain MRI may be negative or show white matter involvement or multifocal involvement of the hippocampus, amygdala, or temporal lobe.

CLASSIFICATION

- HHV-6 and HHV-7 are enveloped, double-stranded DNA viruses that belong to the *Roseolovirus* genus.
- They were the sixth (HHV-6) and seventh (HHV-7) herpesviruses identified.
- They can be distinguished from other herpesviruses by DNA hybridization or by reactions with virus-specific monoclonal antibodies.
- Two subgroups of HHV-6 are distinguishable by their genetic and epidemiologic characteristics.
  - Variant A
  - Variant B
- Although the nucleotide sequences are 90% identical, HHV-6B is the variant typically associated with postnatal childhood illnesses, such as roseola.

SPECIFIC TREATMENTS

- HHV-6 and HHV-7.
  - Acetaminophen is effective in controlling fever.
  - Reassure parents that the rash is a sign of recovery.
- Because infection is self-limited in the immunocompetent child, antiviral therapy is reserved only for life-threatening infection.
- Clinically, antivirals have been used most often in immunocompromised subjects to treat HHV-6 encephalitis, with varying success.
- HHV-6 and HHV-7 have antiviral agent profiles similar to CMV, with limited susceptibility to acyclovir.
  - In vitro studies show that foscarnet, ganciclovir, or cidofovir is somewhat effective.
    - No clinical trials have been conducted with these drugs.
- There are no recommendations for preemptive or prophylactic antivirals for HHV-6 or HHV-7 following HSCT or SOT.

WHEN TO ADMIT

- Hospitalization is usually indicated in infants with a toxic appearance or if there is CNS involvement such as
  - Meningitis
  - Encephalitis
  - Bulging fontanel
  - Recurrent seizures
- Immunocompromised patients may have severe infection with HHV-6 or HHV-7.
  - Typically hospitalized for their severe clinical presentation, for example
    - Pneumonitis
    - Encephalitis
    - Suspected graft-versus-host disease

WHEN TO REFER

- Primary HHV-6 or HHV-7 infections are almost never clinically recognized until the disease is over.
- Referral is rarely needed, except to rule out an alternative diagnosis, such as
  - Seizure disorder
  - Treatable encephalopathy
  - Encephalitis
- Severe clinical symptoms in immunocompromised patients should always be managed by an infectious disease specialist.

COMPLICATIONS

- Long-term sequelae are unusual in the normal child with primary HHV-6 or HHV-7 infection.
- Neurologic damage is occasionally noted in children after complicated seizures associated with either virus.

DEFINITION

- A condition of excessive intracranial cerebrospinal fluid (CSF) volume that disrupts normal brain function and results in increased intracranial pressure, ventriculomegaly, or macrocephaly in children.
- Manifestations are specific to developmental stages.
  - Association with abnormal brain development in the fetus
  - Ventriculomegaly or macrocephaly in the neonate
  - Intracranial hypertension in older children with closed cranial sutures
- Not synonymous with ventriculomegaly.
  - Ventriculomegaly refers to large ventricular size.
  - Hydrocephalus can occur with ventricles of normal size that lack the compliance required for expansion in response to higher pressure.
  - Ventriculomegaly might be a more appropriate term than hydrocephalus in cases for which intracranial pressure is not measurable.
- *Hydrocephalus ex vacuo* refers to an enlargement of the ventricles resulting from brain atrophy without increased intracranial pressure.

SIGNS AND SYMPTOMS

- Acute hydrocephalus.
  - May present with rapidly worsening symptoms
- Chronic conditions.
  - Symptoms depend on the child's stage of development (**Table 1**).
- Routine pediatric physical examinations may reveal
  - Slow compensatory cranial expansion accompanied by delayed suture closure
  - Frontal bossing of the forehead
  - Prominent scalp veins but no neurologic deficits
- In older children, gradual cognitive and motor decline becomes apparent with missed developmental milestones.
- Loss of visual acuity or fields, cranial nerve palsies, and acute papilledema can occur before ventricular dilatation.
- Long-standing hydrocephalus may result in optic atrophy and amblyopia.
  - May confound the evaluation for acute decompensation in affected patients
- L1 syndrome may have the following associated findings:
  - Intellectual disability
  - Adducted thumbs
  - Aqueductal stenosis
  - Spastic paraplegia from pyramidal tract hypoplasia
  - Agenesis of the corpus callosum
- In patients with cognitive deficits, there is no proven relationship between intellectual ability and head circumference or cortical thickness.

DIFFERENTIAL DIAGNOSIS

- Benign isolated macrocephaly or familial macrocephaly.
  - Usual cause of head circumference 2 SDs above the mean or >98th percentile for age in child without signs or symptoms of intracranial hypertension.
  - Presents in an autosomal-dominant pattern within a family.
  - Associated with normal intellectual development.
  - Some cases may have mild suture diastasis that is not associated with intracranial hypertension.
- Benign external hydrocephalus.
  - Normal variant.
  - Imaging studies in the first months of life may demonstrate prominent bifrontal subarachnoid spaces with widened interhemispheric fissures.
- Frontal bossing
  - May cause child's head to seem large despite normal circumference.
  - May occur in cases of cranial hyperostosis, rickets, and liposomal storage disorders.
- Bilateral frontal and parietal prominence resulting in a "box-shaped" skull may herald chronic subdural hematomas (eg, with non-accidental trauma, coagulopathy, or glutaric aciduria type I).
- Relative macrocephaly.
  - <2 SDs above the mean but disproportionately large relative to height and weight.
  - May be caused by short stature, which could be related to intrauterine growth retardation, achondroplasia, or other skeletal dysplasias.
- Macrocephaly is a common reason for a medical genetics referral.
  - Consultations must include evaluation for neuro-cutaneous and systemic stigmata of relevant syndrome associations, such as neurofibromatosis and lysosomal storage diseases.
  - Other conditions to consider include
    - Syndromes of systemic overgrowth (eg, Sotos, Simpson-Golabi-Behmel, Bannayan-Zonana, Weaver, fragile X, macrocephaly-cutis marmorata telangiectatica congenita)
    - Macrocephaly without somatic overgrowth (eg, Opitz-Kaveggia, Greig cephalosyndactyly, acrocallosal syndrome, Gorlin syndrome)

Table 1. Clinical Signs and Symptoms in Pediatric Hydrocephalus

Age Group	Symptoms	Signs
Preterm neonates	Attacks of apnea or bradycardia	• Tense and nonpulsatile anterior fontanel • Distended scalp veins • Abnormal head contour with prominent forehead • Rapid (>1 cm/wk) skull circumference increase
Full-term neonates	• Irritability • Vomiting • Drowsiness	• Full or tense anterior fontanel • Distended scalp veins • Frontal bossing • Widening of cranial sutures • Cracked pot sign on percussion (Macewen sign) • Macrocephaly • Poor head control • Sixth cranial nerve palsy • Setting sun sign (appearance of sclera above iris) • Impairment of upward gaze
Older children	• Steady or progressive headache • Vomiting • Blurred vision, diplopia • Lethargy • Personality and behavior changes	• Papilledema • Spasticity, more in lower limbs • Sixth cranial nerve palsy • Neuroendocrinopathies

DIAGNOSTIC APPROACH

- Neurologic examination in acute hydrocephalus.
  - Focus on whether level of consciousness is sufficient for airway protection and whether immediate neurosurgical consultation for CSF diversion is warranted.
- Normal examination does not rule out intracranial hypertension.
- Careful medical and family history that focuses on
  - Developmental milestones
  - Intellectual and academic ability
  - Visual disturbances
  - Headaches
  - Neurologic symptoms
  - Stigmata of syndromic associations
- Examination should include
  - Objective measurements of head circumference, height, and weight
  - Fundoscopy
  - Visual acuity and fields
  - Assessment of fontanels and sutures
  - Complete neurologic and physical examination
  - Imaging studies
    - Appropriate for developmental stage
    - Used to verify or rule out clinical suspicions
- In some cases, a multidisciplinary approach with neurologic, ophthalmologic, neurosurgical, and medical genetics referrals is warranted.

LABORATORY FINDINGS

- Most useful in cases of suspected infection
  - Cultures and cytology derived from CSF may help diagnose active central nervous system (CNS) infection.

IMAGING

- Skull radiography
  - May demonstrate open sutures and erosion of the dorsum sellae
  - Not generally used for definitive diagnosis
- Ultrasonography
  - Can establish diagnosis in neonate

- Computed tomography (CT)
  - Previously first-line modality in older children for showing ventriculomegaly, interstitial periventricular edema, and sulcal effacement.
  - Calvarial thinning or delayed suture closure may be present in chronic cases.
- Magnetic resonance imaging (MRI)
  - Replacing CT as a first-line modality to avoid excessive radiation exposure.
  - On initial evaluation, MRI is recommended to evaluate for aqueductal stenosis and arachnoid adhesions that would not be obvious on CT.
  - Appropriate for assessing causes of macrocephaly associated with leukoencephalopathy.
    - Alexander and Canavan diseases
    - Childhood ataxia with central hypomyelination/vanishing white matter disease
    - Glutaric aciduria type I
    - L2-hydroxyglutaric aciduria
    - Megalencephalic leukoencephalopathy with subcortical cysts
  - Prenatal MRI is also increasingly available when prenatal ultrasounds are worrisome.

DIAGNOSTIC PROCEDURES

- Lumbar puncture.
  - In the absence of space-occupying mass lesions, may be helpful for identifying increased intracranial pressure.
- Subcutaneous puncture to access the shunt reservoir.
  - In patients with known shunted hydrocephalus, can allow interrogation of the shunt system and collection of CSF for laboratory evaluation
  - Should be used only in rare and specific cases
- In some cases, accessing the intrathecal space accurately identifies a site of flow obstruction.

CLASSIFICATION

- Classified as noncommunicating or communicating, depending on whether there is an identifiable obstruction to CSF circulation.
- This classification scheme is inadequate in patients shunted for hydrocephalus in infancy who later develop severe intracranial hypertension without ventriculomegaly on occasions of shunt failure.
- Some authors advocate a more specific classification system based on the site of obstruction, though, in some cases, aberrant CSF pulsations and subarachnoid compliance may cause hydrocephalus.
- Noncommunicating hydrocephalus.
  - Congenital causes
    - Atresia of the foramen of Monro
    - Chiari malformations
    - Dandy-Walker syndrome
    - Intracranial cysts
    - Aqueductal stenosis
    - Rare genetic syndrome (L1 syndrome)
  - Acquired causes
    - Intraventricular hemorrhage
    - Infectious (bacterial/fungal)
    - Chemical
    - Neoplastic/mass
- Communicating hydrocephalus.
  - Congenital causes
    - Dandy-Walker syndrome
    - Chiari malformations
    - Encephalocele
    - Intracranial cysts
    - Subarachnoid villi noncompliance
  - Acquired causes
    - Infectious (bacterial/fungal)
    - Chemical
    - Leptomeningeal neoplasms
    - Subarachnoid hemorrhage/siderosis

TREATMENT APPROACH

- Management is based on natural history.
- Emergency management of the patient in extremis from acute hydrocephalus requires airway protection and immediate CSF diversion prior to further evaluation.
- Untreated hydrocephalus
  - Upfront untreated mortality is ~50%.
  - Chance of reaching adulthood is ~20%.
  - Most deaths occur <18 months of age.
  - Some untreated patients probably survive because of slow evolution or arrest of their hydrocephalus.
  - Untreated patients have variable disability, from mild visual disturbance and gait abnormalities to blindness, bed confinement, and a requirement for total nursing assistance.
  - Without treatment, ~40% of those few survivors have normal intellect.
- Mortality has decreased to 15% since the advent of shunting.
- Despite the improvement in survival with treatment, only ~50% of those patients have normal intellect and a similar percentage are free of severe behavioral disorders.

- Medical management with agents such as acetazolamide, furosemide, or steroids is mostly ineffective and usually only used as a temporizing measure in mild cases.
- Surgical management.
  - First step is to determine whether an obstruction exists, whereby removal or bypass would reestablish normal CSF circulation.
    - Posterior fossa tumor
    - Arachnoid cyst
    - Aqueductal stenosis
      - Perforation of cisternal barriers (eg, third ventriculostomy) may be performed to restore continuity of flow from the ventricles to the subarachnoid space.
  - Tumors are resected and cysts may be fenestrated.
  - Shunting of multiple compartments may be performed in more complex cases (eg, multiloculated hydrocephalus, Dandy-Walker syndrome).
  - Persistent hydrocephalus.
    - Occurs after resection of obstructive posterior fossa tumors in approximately one-third of cases
    - Requires shunt placement even after normal CSF corridors seem to be reestablished
  - Ventricular dilatation after intraventricular hemorrhage of prematurity.
    - Small neonates may be unable to tolerate placement of a ventriculoperitoneal shunt.
    - CSF diversion is often accomplished in these cases with
      - Serial lumbar or ventricular traps
      - External ventricular drains
      - Ventriculosubgaleal fistulae
      - Subcutaneous ventricular access devices
  - Ventricular size may stabilize after several weeks of these temporizing measures.
    - Ventriculoperitoneal shunt placement is deferred until hydrocephalus is shown to persist after infant weighs ≥2,000 g to improve risk to benefit ratio of surgery.
- Hydrocephalus in the setting of active bacterial CNS infection is managed with
  - Medical treatment and temporary CSF diversion with serial ventricular or lumbar taps
  - Ventriculostomy for continuous external CSF drainage
  - Permanent CSF diversion for persistent hydrocephalus after infection is cleared
  - Multiloculated (complex) hydrocephalus
    - Often related to previous infection
    - Poses a difficult surgical problem, possibly requiring multiple catheter placements and endoscopic procedures
- Hydrocephalus of tubercular origin.
  - Among the most difficult types to manage.
  - Disease process involves thick gelatinous exudates within the basal cisterns and tenacious arachnoid scarring that complicate surgical and endoscopic treatments.
  - Medical management may help clear exudate from the basal cisterns in very select cases.
- Neurocysticercosis.
  - Similarly difficult infection increasingly seen among immigrants to the United States
  - Results in hydrocephalus in 15%–30% of patients with neurologic symptoms

SPECIFIC TREATMENTS

- CSF shunting
  - Permanent diversion from the ventricle to an extracranial absorptive cavity is through a Silastic catheter attached to a 1-way valve and pump/reservoir.
  - Catheter may be accessed with a subcutaneous needle for diagnostic procedures.
  - Valves are selected based on anticipated intracranial pressure.
  - Some valves are magnetically programmable and can be adjusted for changing needs.
  - Common shunt types drain into the peritoneum, pleura, or atrium.
  - Flow-control devices may be included to reduce siphoning effects that occur when the patient is upright.
- Endoscopic third ventriculostomy
  - The floor of the third ventricle and arachnoid membranes of the basal cistern may be perforated with an endoscope introduced through a frontal burr hole.
  - Ideal procedure for
    - Aqueductal stenosis
    - Cases in which shunting is problematic because of repeated infection or failures
    - Hydrocephalus related to pineal region tumors that can be endoscopically biopsied
  - Higher likelihood of success in older patients with aqueductal stenosis, compared with infants with posthemorrhagic hydrocephalus.

WHEN TO ADMIT

- Symptoms of acute or chronic hydrocephalus
- Suspected shunt malfunction/infection in patients with treated hydrocephalus

WHEN TO REFER

- Pediatric neurology referral for macrocephaly with loss of developmental milestones, headaches, or progressive cognitive deficits.
- Ophthalmology consultation for papilledema or suspected deficit in visual acuity or fields.
- Rapid increase in head circumference, crossing growth chart lines, should prompt age-appropriate brain imaging.
- Urgent neurosurgical consultation with radiographic evidence of hydrocephalus.

FOLLOW-UP

- Examination schedule.
  - 2–4 weeks after surgery
  - Every 3 months thereafter for the first year
  - Every 6 months in the second year
  - Then annually or, at some institutions, biannually
- Clinical assessment.
  - Developmental milestones
  - Head circumference
  - Symptoms and signs of increased intracranial pressure or CNS infection
- Adult survivors of childhood hydrocephalus require lifelong follow-up.
- Many patients require shunt surgery during adulthood.
- <4% of patients can be weaned from their shunt.
- Therefore, transition from pediatric to adult care should be coordinated when patients reach the appropriate age.

COMPLICATIONS

- Adverse effects on brain function can range from mechanical distortion or impaired cerebral blood flow to changes in metabolism and neurotransmission.
- Common complications of shunting include
  - Infection
  - Mechanical failure: breaks, kinks, or migration of catheter into ventricle or brain tissue
  - Over-drainage: slit ventricles, subdural hygroma, or chronic subdural hematoma
  - Blockage: proximal or distal, total or partial intermittent
  - Complications specific to ventriculocardiac shunts
    - Thrombosis around the distal tube
    - Cor pulmonale
    - Shunt nephritis
    - Septicemia and pyemic abscesses
  - Complications specific to ventriculopleural shunts
    - Hydrothorax: characterized by respiratory distress
    - Pyothorax
  - Abdominal complications of ventriculoperitoneal shunts
    - Bowel perforation: rare with current catheter materials
    - Pseudocyst: sterile or infected and presenting as obstruction or abdominal swelling
    - Ascites: malabsorption of CSF; sterile or infected
    - Hernia: at shunt insertion incisions
- In patients followed into adulthood, overall incidence of shunt failure is reportedly >80%.
- Hospital admissions for shunt complications are more common than for initial placements.
- Complications are more common in children with shunts from preterm birth.
  - Increased risk of slit ventricle syndrome, loculated hydrocephalus, and infection
- Most common cause of shunt failure is obstruction of the proximal catheter, usually caused by infiltration by choroid plexus.
- Shunt obstruction.
  - Overall incidence of shunt obstruction is ~40% during the first year; 45% with posthemorrhagic hydrocephalus.
  - Prior to surgical exploration, it may be difficult to determine whether obstruction is at the proximal or distal catheter or at the valve.
    - Depressed reservoir that cannot be pumped or tapped may indicate a proximal obstruction.
    - On the other hand, small ventricles may collapse around a functioning catheter, making the reservoir unable to be pumped without a true obstruction.
    - Ability to pump a reservoir does not rule out obstruction, as functional blockage could potentially be overcome by manual pumping.
  - Tapping the shunt is only indicated in rare and specific cases.
    - Most obstructions can be diagnosed correctly by other means.
    - For programmable shunts, first step should be to investigate the setting to ensure that it has not been inadvertently changed.

- Over-drainage.
  - Common complication that results in headaches from intracranial hypotension.
  - Can lead to subdural hematomas or hygromas, especially with cases of severe cortical thinning.
  - Anti-siphon valves and programmable shunts have been designed to help alleviate this problem, but it remains common.
    - With programmable shunts, the first step is to increase resistance in the valve.
- Infection.
  - Frequent complication of shunting.
  - Usually involves skin flora, such as *Staphylococcus epidermidis, Propionibacterium acnes*, and *Staphylococcus aureus.*
  - Younger age is a risk factor for infection; the overall rate in infants is ~7%.
  - Treatment requires explantation of the shunt system with temporary external drainage and intravenous antibiotics.
    - Shunts are reinserted following clearance of infection, as documented by negative culture results.

PROGNOSIS

- In chronic cases, patients may have a good quality of life punctuated by unexpected therapeutic failures, repeated medical evaluations, and surgical procedures.
- Etiology of hydrocephalus and timing of surgical treatment are among the most important prognostic factors for outcome.
  - Almost impossible to determine independent long-term effects because of varied etiology.
  - Congenital and acquired causes may have deleterious effects apart from hydrocephalus, such as dysgenesis of the corpus callosum.
- Possible direct effects of hydrocephalus from any cause.
  - Ependymal destruction
  - Compression and collapse of cerebral vasculature
  - White matter displacement
  - Cortical neuronal injury
- Shunt malfunction.
  - Permanent risk.
  - Most patients require reoperations into adulthood.
- Endoscopic third ventriculostomy.
  - Alternative to shunting; carries a risk of delayed rapid deterioration that may be fatal
- Early studies failed to find a relationship between brain cortical thickness and intellectual ability.
  - Effect of these anatomic features cannot be isolated from the contributions of associated medical comorbidities and exposures to repeated surgical procedures and their complications.

PREVENTION

- Reduction of modifiable risk factors through prenatal care and campaigns to decrease endemic infections.
- Efforts are underway by multicenter networks to establish standard procedure protocols to reduce shunt complications.

DEFINITION

- Hyperhidrosis is excessive, localized palmoplantar or axillary sweating beyond the norm for thermoregulation.

HISTORY

- The child or family reports
  - Odiferous sweating.
  - Sweating so intense that it interferes with
    - Hand functions
    - Foot functions
  - Axillary hyperhidrosis in adolescence may cause embarrassment.
    - Sweat ring on clothing
    - Odor associated with bacterial degradation of apocrine sweat

DIFFERENTIAL DIAGNOSIS

- Excessive generalized sweating, not limited to the palms, soles, and axillae, may be caused by a systemic disorder.
  - Infection
  - Hypoglycemia
  - Drug withdrawal
  - Lymphoma
  - Thyrotoxicosis
  - Pheochromocytoma
  - Dysautonomia (Riley-Day syndrome)

TREATMENT APPROACH

- Topical and systemic agents include
  - Anticholinergic agents
  - Prescription 20% aluminum chloride
  - Tap water iontophoresis
- For bromhidrosis (malodorous hyperhidrosis) of the soles
  - Frequent cleansing with drying deodorant soaps
  - Topical antibiotics
  - Going barefoot whenever possible
- For combined axillary hyperhidrosis and bromhidrosis
  - Frequent clothing changes
  - Topical antibiotics and deodorant powders
- For sweating caused by emotional stress
  - Propranolol and anxiolytics
- Management of primary palmoplantar and axillary hyperhidrosis may decrease risk for associated
  - Infection such as warts, dermatophytosis, and pitted keratolysis
  - Eczematous dermatitis
- Use of significant measures may be supported by improved quality of life.

SPECIFIC TREATMENT

Pharmacologic Treatment

- Systemic anticholinergic agents.
  - May block acetylcholine, the sympathetic innervation terminal neurotransmitter to eccrine glands.
  - Side effects preclude long-term use.
- Prescription 20% aluminum chloride.
  - Application every other day for palmar sweating or plantar hyperhidrosis
  - Prescription 20% solution of aluminum chloride in anhydrous ethanol applied to the axillary vault
    - May cause an irritant contact dermatitis
    - Hydrocortisone 1% cream for relief of inflammation
- Propranolol and anxiolytics are options to reduce emotional stress.
- Botulinum A toxin.
  - Approved for axillary sweat gland chemodenervation
  - Palmar and plantar hyperhidrosis
    - Subepidermal injections inhibit sweat production.
    - Purportedly blocks presynaptic acetylcholine release.
    - Effective for up to 12 months.
    - Has been used in patients as young as 14 years.
    - Causes temporary or, rarely, permanent muscle and nerve injury from the injections.

Other Measures

- In extreme cases
  - Excision of local axillary skin
  - Removal of glands by curettage or liposuction
    - Ganglion sympathectomy cannot be recommended for most patients who have axillary hyperhidrosis because of attendant complications.

WHEN TO REFER

- Hyperhidrosis that interferes with appropriate bodily function (eg, hand so slippery wet that the child cannot hold a pencil)
- Generalized excessive sweating
- Socially isolating hyperhidrosis as a result of odor or excessive drenching of clothing

DEFINITION

- In children and adolescents, hypertension is defined as elevated blood pressure (BP) that persists on repeated measurement at ≥95th percentile for age, height, and sex in a healthy population.
- Stage 1 hypertension.
  - Systolic and diastolic BPs that range from ~95th percentile to 5 mm Hg above the 99th percentile
- Stage 2 hypertension.
  - Systolic and diastolic BPs that are 5 mm Hg above the 99th percentile for age, height, and sex
- High-normal or prehypertensive BP.
  - BP between the 90th and 95th percentiles (Normal systolic and diastolic BPs are <90th percentile.)
- Severe hypertension (with the risk of end organ injury) is defined as BP >99th percentile.
- Body size is the single most important determinant of BP in children and adolescents.
  - Using accurate height percentiles is critical for correctly estimating BP percentiles.
- 2 categories of hypertension.
  - Primary (previously termed "essential")
  - Secondary

HISTORY

- Medical history should include questions about
  - All cardiovascular risk factors
  - Symptoms suggestive of secondary hypertension
  - Possible target organ damage
- Particular attention needs to be paid to any history suggesting
  - Recent onset of renal disease
  - Chronic urinary tract infections (UTIs)
- In adolescents, use of the following substances should be explored:
  - Exogenous steroids
  - Oral contraceptives
  - Illicit drugs
  - Tobacco
  - Alcohol
- A systems review that includes the following details:
  - Diet
  - Salt intake
  - Exercise
- A history of any of the following conditions may be helpful in directing further evaluations:
  - Preterm birth
  - Patent ductus arteriosus
  - Bronchopulmonary dysplasia
- A positive family history, including age of onset, of
  - Primary hypertension
  - Systemic disease
  - Endocrinopathy

PHYSICAL EXAMINATION

BP Measurement

- Systolic BP: pressure at the onset of the first Korotkoff sound.
- Diastolic BP: pressure at the fifth Korotkoff sound or at the disappearance or muffling of the Korotkoff sounds.
  - In some children, Korotkoff sounds can be heard until 0 mm Hg.
  - Measurement can be repeated with less pressure on the head of the stethoscope; if fifth Korotkoff sound continues to identify very low pressures, the fourth sound can be recorded.
- Height and weight are related independently to BP at all ages (**Tables 1** and **2**).
- Measure BP in all children >3 years.
- High risk factors that warrant BP measurement before 3 years include[1]
  - Preterm birth, very low birth weight, history of neonatal hypertension, or other neonatal complications requiring intensive care
  - Congenital heart disease (repaired or non-repaired)
  - Recurrent UTIs, hematuria, proteinuria
  - Renal disease or urologic malformations
  - Family history of congenital renal disease
  - Solid-organ transplantation
  - Malignancy or bone marrow transplantation
  - Treatment with drugs known to increase BP
  - Other systemic illnesses associated with hypertension
  - Evidence of elevated intracranial pressure
- Appropriate techniques are important to avoid false-positive readings.
  - Screening BP should be measured in the right arm for consistency and comparison with standardized tables.
  - Infants should be supine.
  - Children and adolescents should be seated.
    - Child should be quiet for 5 minutes before measurement.
    - Back should be supported and feet on the floor.
    - Right arm should be supported, with antecubital fossa at heart level.
    - Child should not have recently ingested stimulant drugs or food.

(continued on page 523)

Table 1. Blood Pressure and Height Percentiles for Boys by Age

Age (Yr)	BP Percentile[a]	Systolic BP (mm Hg)							Diastolic BP (mm Hg)						
		Percentile of Height							Percentile of Height						
		5	10	25	50	75	90	95	5	10	25	50	75	90	95
1	50	80	81	83	85	87	88	89	34	35	36	37	38	39	39
	90	94	95	97	99	100	102	103	49	50	51	52	53	53	54
	95	98	99	101	103	104	106	106	54	54	55	56	57	58	58
	99	105	106	108	110	112	113	114	61	62	63	64	65	66	66
2	50	84	85	87	88	90	92	92	39	40	41	42	43	44	44
	90	97	99	100	102	104	105	106	54	55	56	57	58	58	59
	95	101	102	104	106	108	109	110	59	59	60	61	62	63	63
	99	109	110	111	113	115	117	117	66	67	68	69	70	71	71
3	50	86	87	89	91	93	94	95	44	44	45	46	47	48	48
	90	100	101	103	105	107	108	109	59	59	60	61	62	63	63
	95	104	105	107	109	110	112	113	63	63	64	65	66	67	67
	99	111	112	114	116	118	119	120	71	71	72	73	74	75	75
4	50	88	89	91	93	95	96	97	47	48	49	50	51	51	52
	90	102	103	105	107	109	110	111	62	63	64	65	66	66	67
	95	106	107	109	111	112	114	115	66	67	68	69	70	71	71
	99	113	114	116	118	120	121	122	74	75	76	77	78	78	79
5	50	90	91	93	95	96	98	98	50	51	52	53	54	55	55
	90	104	105	106	108	110	111	112	65	66	67	68	69	69	70
	95	108	109	110	112	114	115	116	69	70	71	72	73	74	74
	99	115	116	118	120	121	123	123	77	78	79	80	81	81	82

Table 1 (*continued*)

Age (Yr)	BP Percentile[a]	Systolic BP (mm Hg)							Diastolic BP (mm Hg)						
		Percentile of Height							Percentile of Height						
		5	10	25	50	75	90	95	5	10	25	50	75	90	95
6	50	91	92	94	96	98	99	100	53	53	54	55	56	57	57
	90	105	106	108	110	111	113	113	68	68	69	70	71	72	72
	95	109	110	112	114	115	117	117	72	72	73	74	75	76	76
	99	116	117	119	121	123	124	125	80	80	81	82	83	84	84
7	50	92	94	95	97	99	100	101	55	55	56	57	58	59	59
	90	106	107	109	111	113	114	115	70	70	71	72	73	74	74
	95	110	111	113	115	117	118	119	74	74	75	76	77	78	78
	99	117	118	120	122	124	125	126	82	82	83	84	85	86	86
8	50	94	95	97	99	100	102	102	56	57	58	59	60	60	61
	90	107	109	110	112	114	115	116	71	72	72	73	74	75	76
	95	111	112	114	116	118	119	120	75	76	77	78	79	79	80
	99	119	120	122	123	125	127	127	83	84	85	86	87	87	88
9	50	95	96	98	100	102	103	104	57	58	59	60	61	61	62
	90	109	110	112	114	115	117	118	72	73	74	75	76	76	77
	95	113	114	116	118	119	121	121	76	77	78	79	80	81	81
	99	120	121	123	125	127	128	129	84	85	86	87	88	88	89
10	50	97	98	100	102	103	105	106	58	59	60	61	61	62	63
	90	111	112	114	115	117	119	119	73	73	74	75	76	77	78
	95	115	116	117	119	121	122	123	77	78	79	80	81	81	82
	99	122	123	125	127	128	130	130	85	86	86	88	88	89	90

Table 1 (*continued*)

Age (Yr)	BP Percentile[a]	Systolic BP (mm Hg)							Diastolic BP (mm Hg)						
		Percentile of Height							Percentile of Height						
		5	10	25	50	75	90	95	5	10	25	50	75	90	95
11	50	99	100	102	104	105	107	107	59	59	60	61	62	63	63
	90	113	114	115	117	119	120	121	74	74	75	76	77	78	78
	95	117	118	119	121	123	124	125	78	78	79	80	81	82	82
	99	124	125	127	129	130	132	132	86	86	87	88	89	90	90
12	50	101	102	104	106	108	109	110	59	60	61	62	63	63	64
	90	115	116	118	120	121	123	123	74	75	75	76	77	78	79
	95	119	120	122	123	125	127	127	78	79	80	81	82	82	83
	99	126	127	129	131	133	134	135	86	87	88	89	90	90	91
13	50	104	105	106	108	110	111	112	60	60	61	62	63	64	64
	90	117	118	120	122	124	125	126	75	75	76	77	78	79	79
	95	121	122	124	126	128	129	130	79	79	80	81	82	83	83
	99	128	130	131	133	135	136	137	87	87	88	89	90	91	91
14	50	106	107	109	111	113	114	115	60	61	62	63	64	65	65
	90	120	121	123	125	126	128	128	75	76	77	78	79	79	80
	95	124	125	127	128	130	132	132	80	80	81	82	83	84	84
	99	131	132	134	136	138	139	140	87	88	89	90	91	92	92
15	50	109	110	112	113	115	117	117	61	62	63	64	65	66	66
	90	122	124	125	127	129	130	131	76	77	78	79	80	80	81
	95	126	127	129	131	133	134	135	81	81	82	83	84	85	85
	99	134	135	136	138	140	142	142	88	89	90	91	92	93	93

Table 1 (*continued*)

Age (Yr)	BP Percentile[a]	Systolic BP (mm Hg)							Diastolic BP (mm Hg)						
		Percentile of Height							Percentile of Height						
		5	10	25	50	75	90	95	5	10	25	50	75	90	95
16	50	111	112	114	116	118	119	120	63	63	64	65	66	67	67
	90	125	126	128	130	131	133	134	78	78	79	80	81	82	82
	95	129	130	132	134	135	137	137	82	83	83	84	85	86	87
	99	136	137	139	141	143	144	145	90	90	91	92	93	94	94
17	50	114	115	116	118	120	121	122	65	66	66	67	68	69	70
	90	127	128	130	132	134	135	136	80	80	81	82	83	84	84
	95	131	132	134	136	138	139	140	84	85	86	87	87	88	89
	99	139	140	141	143	145	146	147	92	93	93	94	95	96	97

Abbreviation: BP, blood pressure.

[a] The 90th, 95th, and 99th percentiles are 1.280, 1.645, and 2.326 standard deviations, respectively, above the mean.

From National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents. The fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents. *Pediatrics.* 2004;114(2 Suppl 2):555–576.

Table 2. Blood Pressure and Height Percentiles for Girls by Age

Age (Yr)	BP Percentile[a]	Systolic BP (mm Hg)							Diastolic BP (mm Hg)						
		Percentile of Height							Percentile of Height						
		5	10	25	50	75	90	95	5	10	25	50	75	90	95
1	50	83	84	85	86	88	89	90	38	39	39	40	41	41	42
	90	97	97	98	100	101	102	103	52	53	53	54	55	55	56
	95	100	101	102	104	105	106	107	56	57	57	58	59	59	60
	99	108	108	109	111	112	113	114	64	64	65	65	66	67	67
2	50	85	85	87	88	89	91	91	43	44	44	45	46	46	47
	90	98	99	100	101	103	104	105	57	58	58	59	60	61	61
	95	102	103	104	105	107	108	109	61	62	62	63	64	65	65
	99	109	110	111	112	114	115	116	69	69	70	70	71	72	72
3	50	86	87	88	89	91	92	93	47	48	48	49	50	50	51
	90	100	100	102	103	104	106	106	61	62	62	63	64	64	65
	95	104	104	105	107	108	109	110	65	66	66	67	68	68	69
	99	111	111	113	114	115	116	117	73	73	74	74	75	76	76
4	50	88	88	90	91	92	94	94	50	50	51	52	52	53	54
	90	101	102	103	104	106	107	108	64	64	65	66	67	67	68
	95	105	106	107	108	110	111	112	68	68	69	70	71	71	72
	99	112	113	114	115	117	118	119	76	76	76	77	78	79	79
5	50	89	90	91	93	94	95	96	52	53	53	54	55	55	56
	90	103	103	105	106	107	109	109	66	67	67	68	69	69	70
	95	107	107	108	110	111	112	113	70	71	71	72	73	73	74
	99	114	114	116	117	118	120	120	78	78	79	79	80	81	81

Table 2 (*continued*)

Age (Yr)	BP Percentile[a]	Systolic BP (mm Hg)							Diastolic BP (mm Hg)						
		Percentile of Height							Percentile of Height						
		5	10	25	50	75	90	95	5	10	25	50	75	90	95
6	50	91	92	93	94	96	97	98	54	54	55	56	56	57	58
	90	104	105	106	108	109	110	111	68	68	69	70	70	71	72
	95	108	109	110	111	113	114	115	72	72	73	74	74	75	76
	99	115	116	117	119	120	121	122	80	80	80	81	82	83	83
7	50	93	93	95	96	97	99	99	55	56	56	57	58	58	59
	90	106	107	108	109	111	112	113	69	70	70	71	72	72	73
	95	110	111	112	113	115	116	116	73	74	74	75	76	76	77
	99	117	118	119	120	122	123	124	81	81	82	82	83	84	84
8	50	95	95	96	98	99	100	101	57	57	57	58	59	60	60
	90	108	109	110	111	113	114	114	71	71	71	72	73	74	74
	95	112	112	114	115	116	118	118	75	75	75	76	77	78	78
	99	119	120	121	122	123	125	125	82	82	83	83	84	85	86
9	50	96	97	98	100	101	102	103	58	58	58	59	60	61	61
	90	110	110	112	113	114	116	116	72	72	72	73	74	75	75
	95	114	114	115	117	118	119	120	76	76	76	77	78	79	79
	99	121	121	123	124	125	127	127	83	83	84	84	85	86	87

Table 2 (*continued*)

Age (Yr)	BP Percentile[a]	Systolic BP (mm Hg)							Diastolic BP (mm Hg)						
		Percentile of Height							Percentile of Height						
		5	10	25	50	75	90	95	5	10	25	50	75	90	95
10	50	98	99	100	102	103	104	105	59	59	59	60	61	62	62
	90	112	112	114	115	116	118	118	73	73	73	74	75	76	76
	95	116	116	117	119	120	121	122	77	77	77	78	79	80	80
	99	123	123	125	126	127	129	129	84	84	85	86	86	87	88
11	50	100	101	102	103	105	106	107	60	60	60	61	62	63	63
	90	114	114	116	117	118	119	120	74	74	74	75	76	77	77
	95	118	118	119	121	122	123	124	78	78	78	79	80	81	81
	99	125	125	126	128	129	130	131	85	85	86	87	87	88	89
12	50	102	103	104	105	107	108	109	61	61	61	62	63	64	64
	90	116	116	117	119	120	121	122	75	75	75	76	77	78	78
	95	119	120	121	123	124	125	126	79	79	79	80	81	82	82
	99	127	127	128	130	131	132	133	86	86	87	88	88	89	90
13	50	104	105	106	107	109	110	110	62	62	62	63	64	65	65
	90	117	118	119	121	122	123	124	76	76	76	77	78	79	79
	95	121	122	123	124	126	127	128	80	80	80	81	82	83	83
	99	128	129	130	132	133	134	135	87	87	88	89	89	90	91
14	50	106	106	107	109	110	111	112	63	63	63	64	65	66	66
	90	119	120	121	122	124	125	125	77	77	77	78	79	80	80
	95	123	123	125	126	127	129	129	81	81	81	82	83	84	84
	99	130	131	132	133	135	136	136	88	88	89	90	90	91	92

Table 2 (*continued*)

Age (Yr)	BP Percentile[a]	Systolic BP (mm Hg)							Diastolic BP (mm Hg)						
		Percentile of Height							Percentile of Height						
		5	10	25	50	75	90	95	5	10	25	50	75	90	95
15	50	107	108	109	110	111	113	113	64	64	64	65	66	67	67
	90	120	121	122	123	125	126	127	78	78	78	79	80	81	81
	95	124	125	126	127	129	130	131	82	82	82	83	84	85	85
	99	131	132	133	134	136	137	138	89	89	90	91	91	92	93
16	50	108	108	110	111	112	114	114	64	64	65	66	66	67	68
	90	121	122	123	124	126	127	128	78	78	79	80	81	81	82
	95	125	126	127	128	130	131	132	82	82	83	84	85	85	86
	99	132	133	134	135	137	138	139	90	90	90	91	92	93	93
17	50	108	109	110	111	113	114	115	64	65	65	66	67	67	68
	90	122	122	123	125	126	127	128	78	79	79	80	81	81	82
	95	125	126	127	129	130	131	132	82	83	83	84	85	85	86
	99	133	133	134	136	137	138	139	90	90	91	91	92	93	93

Abbreviation: BP, blood pressure.

[a] The 90th, 95th, and 99th percentiles are 1.280, 1.645, and 2.326 standard deviations, respectively, above the mean.

From National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents. The fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents. *Pediatrics.* 2004;114(2 Suppl 2):555–576.

- Appropriately sized cuff.
  - Width of cuff must be ≥40% of the mid-arm circumference, as measured midway between the olecranon and the acromion.
  - Cuff should be long enough to cover ≥80% of the circumference of the arm.
  - Cuff should be inflated to ≥30 mm Hg above the expected systolic BP.
  - Pressure that is too high in young children or infants may cause agitation.
  - Stethoscope or Doppler crystal should be placed lightly over the brachial artery in the antecubital fossa.
  - Arm should be at the level of the heart.
- When hypertension is suspected, measure BP in all 4 extremities.
  - Average of at least 2 separate measurements
  - Average 2 systolic and 2 diastolic readings
  - Best to average measurements obtained on 3 separate occasions
- Assess radial, brachial, and, most importantly, femoral pulses.

- Automated BP devices.
  - In general, auscultation is the recommended method of measuring BP in children.
  - Advantages of automated measurement include
    - Relative simplicity.
    - Minimization of observer bias and terminal digit preferences.
    - Provides serial noninvasive BP in newborns and infants, in whom auscultation is difficult.
    - Good in the intensive care unit, where frequent BP measurements are needed.
    - Automated measurements seem to correlate well with intraarterial readings.
  - Reliability in the physician's office is less clear.
    - Devices require frequent calibration.
    - Reference standards have not been established.
    - May overestimate BP and incidence of hypertension.

Complete Physical Examination

- Calculation of body mass index
  - Weight in kilograms divided by the square of height in meters
- Auscultation for carotid, abdominal, and femoral bruits
- Palpation of the thyroid gland
- Thorough examination of the heart and lungs
- Examination of the abdomen for
  - Enlarged kidneys
  - Masses
  - Abnormal aortic pulsation
- Palpation of the legs for edema and pulses
- Examination of the optic fundi
- Cutaneous examination for lesions associated with hypertension (eg, café au lait spots)
- Neurologic assessment
- Hypertensive neonates often have evidence of
  - Congestive heart failure
  - Respiratory distress
  - Feeding difficulties
  - Irritability
  - Lethargy
  - Coma

DIFFERENTIAL DIAGNOSIS

General

- Primary hypertension is often seen in patients with
  - Obesity
  - Positive family history of hypertension or cardiovascular disease

Causes of Secondary Hypertension in Neonates and Infants

- Renal artery thrombosis after umbilical artery catheterization
- Coarctation of the aorta
- Congenital renal parenchymal or structural disease
- Renal artery stenosis
- Bronchopulmonary dysplasia
- Patent ductus arteriosus
- Increased intracranial pressure
- Extracorporeal membrane oxygenation

Causes of Secondary Hypertension in Children and Adolescents

- In most children, hypertension is secondary to renal or renovascular causes.
  - Renal parenchymal disease
    - The most frequent cause of hypertension in childhood
    - Accounts for 60%–80% of cases
  - Renal artery stenosis, caused by
    - Fibromuscular dysplasia.
    - Takayasu arteritis.
    - Williams syndrome.
    - Neurofibromatosis.

- — Children with renal artery stenosis may have marked symptoms caused by end-organ damage.
  - Congestive heart failure
  - Left ventricular hypertrophy
  - Retinal changes
  - Renal impairment
- Acute poststreptococcal glomerulonephritis
  - — Hypertension is evident at the initial diagnosis in almost 80% of all cases.
  - — Of those who are normotensive at first, nearly one-half will experience hypertension during the course of their illness.
- Membranoproliferative glomerulonephritis
- Diffuse proliferative glomerulonephritis
- Lupus nephritis
- Immunoglobulin A nephropathy
- Hemolytic uremic syndrome
- Nephrotic syndrome
  - — Rarely leads to severe hypertension, unless it is a manifestation of more serious renal disease
- Reflux nephropathy (prevalence of 5%–30%)
- Polycystic kidney disease
- Wilms tumor

- Coarctation of the aorta.
  - The most common nonrenal cause of hypertension in childhood.
  - Accounts for 5%–15% of cases.
  - Hypertension can also occur immediately after repair of coarctation of the aorta and for years thereafter.
  - Risk for postoperative hypertension appears to be lower if the lesion is repaired before 5 years.
- Obstructive sleep apnea.
- Endocrine disorders.
  - Mineralocorticoid excess
  - Hyperthyroidism
  - Pheochromocytoma
  - Hypercalcemia
  - Adrenal cortical hyperplasia
- Nervous system disorders.
  - Neurogenic tumors
  - Increased intracranial pressure
- Drug related.
  - Ingestion or abuse of glucocorticoids or other steroids
  - Oral contraceptives in adolescent girls
  - Sympathomimetics
    - — Amphetamines
    - — Cocaine
    - — Phenylephrine
    - — Pseudoephedrine
  - Nonsteroidal anti-inflammatory drugs
  - Erythropoietin
  - Cyclosporine
- Immobilization-induced hypertension.
- Metabolic syndrome is a constellation of risk factors, including
  - Elevated systolic or diastolic BP
  - Elevated plasma triglyceride level
  - Low high-density lipoprotein cholesterol level
  - Insulin resistance
  - Large waist circumference
  - Associated with onset of type 2 diabetes and long-term atherosclerotic cardiovascular complications
    - — A child might have metabolic syndrome if ≥3 risk factors are present.

LABORATORY EVALUATION

- General laboratory screening for possible renal dysfunction, including
  - Urinalysis
  - Complete blood cell count
  - Serum urea nitrogen
  - Creatinine
  - Serum electrolytes (including glucose)
  - Urine culture (possibly)
- Positive family history of primary hypertension
  - Lipid profile, including
    - — High-density lipoprotein cholesterol
    - — Low-density lipoprotein cholesterol
    - — Triglycerides (to assess cardiovascular risk)
- If BP remains elevated after initial treatment, more intensive investigations should include
  - Plasma renin activity for suspected renovascular disease or mineralocorticoid excess
  - Thyroid function test for possible hyperthyroidism
  - Serum catecholamines for suspected pheochromocytoma

IMAGING

- Imaging of the genitourinary system if a renal cause is suspected
  - Color Doppler ultrasound of aorta and renal vessels
    - — Detects aortic, renal venous and arterial thrombi

- Renal ultrasound
  - Congenital and parenchymal abnormalities
- Nuclear scintigraphy with angiotensin-converting enzyme (ACE) inhibition
  - For differential renal function and prediction of renal functional deterioration
- High-resolution contrast-enhanced computed tomographic angiography
  - 3-dimensional views of renal arteries
- Magnetic resonance angiography with gadolinium
- Digital subtraction angiography
  - The gold standard for visualization of renovascular hypertension

■ Echocardiography
- May identify coarctation of the aorta
- Will provide information about left ventricular mass
  - Left ventricular hypertrophy is the most prominent evidence of target-organ damage.
  - At diagnosis and for regular follow-up of children with established hypertension.

DIAGNOSTIC PROCEDURES

■ Ambulatory BP monitoring
- Used to help establish the diagnosis of hypertension and to track diurnal variations of BP in older children.
- Should be used and interpreted only by those experienced in pediatric hypertension.
- A monitor is worn on the arm for 24 hours.
- BP is measured regularly throughout the day and night.
- Specifically helpful in evaluating
  - White-coat hypertension
  - Risk for hypertensive end-organ injury
  - Efficacy of treatment and possible drug resistance
  - Masked hypertension
  - Hypotension that may occur with antihypertensive drug treatment
  - BP patterns in such conditions as
    - Episodic hypertension
    - Chronic kidney disease
    - Diabetes
    - Autonomic dysfunction
- BP typically decreases by >10% during sleep.
  - Absence of this decrease is strongly associated with masked hypertension and end-organ damage.
- Systolic and diastolic BPs >95th percentile in >25% of ambulatory measurements are considered abnormal and require treatment.

■ Cardiac evaluation
- Femoral pulse, electrocardiography, echocardiography

■ Formal stress testing
- To assess normal and abnormal BP responses to exercise
- May be especially helpful in young athletes

TREATMENT APPROACH

■ Mild to moderate hypertension in childhood is generally not associated with marked symptoms.
- BP elevation at this level almost certainly warrants
  - Close attention
  - Lifestyle modifications
  - Possible therapy

■ For children with chronic primary hypertension but no hypertensive target-organ damage
- The goal should be to reduce BP to <95th percentile for age, sex, and height.

■ For children with chronic renal disease, diabetes, or hypertensive target-organ damage
- The goal should be to reduce BP to <90th percentile for age, sex, and height.

■ Justification for treating children who have marked hypertension comes from the results of adult trials.
- Reduction of BP reduces the risk of target-organ damage.
- Definitive therapy can decrease later morbidity.

SPECIFIC TREATMENT

Therapeutic Lifestyle Changes

■ Low-salt or no-added-salt diet

■ Increased intake of
- Fresh vegetables
- Fruits
- Fiber
- Low-fat dairy products

■ Weight loss
- Weight loss is often associated with reduction in systolic and diastolic pressures.
- Maintaining normal weight in childhood reduces the likelihood of high BP in adulthood.
- Weight loss also is associated with
  - Decreased BP sensitivity to salt
  - Decreased dyslipidemia and insulin resistance
- Focus on health reasons for weight loss instead of appearance.

- Exercise
  - Adjunct to weight loss.
  - Often reduces BP even more than weight loss alone.
  - Increasing regular physical activity and decreasing sedentary activities are important in preventing hypertension.

Pharmacologic Therapy

- Indicated in children and adolescents who
  - Do not respond to lifestyle modifications.
  - Have such conditions as
    - Stage 2 systemic hypertension
    - Secondary hypertension
    - Established hypertensive target-organ damage
- All classes of antihypertensive drugs lower BP in children.
  - Choice of therapy depends on underlying etiology (**Table 3**).
    - Renin or non-renin mediated
    - Volume dependent
- Basic strategy.
  - Start with a single drug and assess response.
  - Add additional drugs one at a time, always attempting to target a different mechanism.
- Drug of first choice in primary hypertension.
  - ACE inhibitor or a calcium channel blocker.
  - ACE inhibitors and receptor blockers are useful in proteinuric renal disease but should be used with caution in female adolescents because of risk for ACE inhibitor fetopathy.
  - Angiotensin blockers and calcium channel blockers have the fewest adverse effects in physically active adolescents.
- β-Blockers.
  - Tend to produce more side effects.
  - Non-cardioselective β-blockers.
    - Can cause hypoglycemia after intense exercise
    - Particularly problematic with reactive airway disease and diabetes

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Table 3. Antihypertensive Drugs Commonly Used to Manage Chronic Hypertension in Children

Drug	Initial Dose (mg/kg/d)	Maximal Dose	Interval (times/d)
ACE Inhibitors			
Benazepril[a]	0.2	40 mg	1
Captopril[b]	0.15–0.50	6 mg/kg/d	3–4
Enalapril[b]	0.08–0.50	40 mg	1–2
Fosinopril[a]	0.1–0.6	40 mg	1
Lisinopril[a]	0.07	40 mg	1
Angiotensin Receptor Blockers			
Irbesartan[a]			
6–12 y	2	75–150 mg	1–2
≥13 y	2	150–300 mg	1–2
Losartan[a]	0.7	100 mg	1–2
Candesartan	0.05–0.40	32 mg	1–2
Valsartan[a]	1.3	160 mg	1
α- and β-Blockers			
Labetalol	1–4	1,200 mg	2
Atenolol	0.5–1.2	100 mg	1
Bisoprolol/HCTZ[a]	2.5/6.25 mg/d	10/6.25 mg	1

Table 3 (*continued*)

Drug	Initial Dose (mg/kg/d)	Maximal Dose	Interval (times/d)
α- and β-Blockers (*continued*)			
Metoprolol	1–2	200 mg	1–2
Propranolol	1–4	640 mg	2–4
Calcium Channel Blockers			
Amlodipine	0.1–0.6	20 mg	1–2
Felodipine[a]	2.5 mg/d	10 mg	1
Isradipine	0.15–0.20/dose	20 mg	2–4
Extended-release nifedipine	0.25–0.50	120 mg	1
Central α-Agonist			
Clonidine (≥12 y)	0.05–0.2 mg/d	2.4 mg	2–4
Diuretics			
HCTZ	1–4	200 mg	1–2
Furosemide	0.5–2.0	6 mg/kg/dose	2–4
Spironolactone	1.0–3.3	200 mg	2–4
Amiloride	0.400–0.625	20 mg	1
Vasodilators			
Hydralazine	0.75–1.0	200 mg	2–4
Minoxidil	0.1–0.5 mg/kg/dose	20 mg	2

Abbreviations: ACE, angiotensin-converting enzyme; HCTZ, hydrochlorothiazide.

[a] Not recommended before age 6 years.
[b] The lowest effective dose of these drugs is used in neonates because it can cause acute deterioration in renal function.

- β-blockers and calcium channel blockers can be used with hypertension and migraine.
- β-blockers should not be used in active athletes because they decrease cardiac contractility, heart rate, and maximum oxygen uptake.

- α-Agonists.
  - Generally considered to be second-line drugs
- Diuretics.
  - Now used less often for initial therapy of chronic hypertension
  - Not desirable in active athletes because of risk for hypovolemia and hypokalemia
  - Useful in volume-dependent hypertension, as with poststreptococcal glomerulonephritis
- For patients with elevated intracranial pressure, hypertension should be treated judiciously.

WHEN TO REFER

- Stage 1 hypertension
- Stage 2 hypertension
- Specific conditions requiring referral
- Symptomatic primary hypertension
- Secondary hypertension
- Hypertension with diabetes
- Evidence of target-organ damage (left ventricular hypertrophy)
- Neonatal hypertension

WHEN TO ADMIT

- Hypertensive emergencies associated with manifestations in other organs
- Hypertensive urgencies (severe BP elevation without other organ involvement)

- Specific conditions requiring admission
- Acute glomerular diseases
- Poststreptococcal glomerulonephritis
- Hemolytic uremic syndrome
- Renal artery stenosis
- Fibromuscular dysplasia
- Previous umbilical artery catheter
- Neurofibromatosis
- Pheochromocytoma
- Coarctation of aorta
- Noncompliance with current antihypertensive medication
- Cocaine toxicity
- Dialysis patients with excessive volume expansion

FOLLOW-UP

- Stage 1 hypertension
- Monitor every 3 to 6 months.
- Stage 2 hypertension
- Monitor more closely depending on degree of control.
- Athletic participation by children with hypertension
- Encourage noncompetitive sports and aerobic exercise in all.
  - Prehypertension.
    - No restriction, can participate in competitive sports
  - Stage 1 hypertension.
    - No restriction, can participate in competitive sports if no end-organ damage
  - Stage 2 hypertension.
    - Restriction from high static sports.
    - Eligible for competitive sports depending on extent of cardiac disease.
    - Encourage aerobic exercises with intensity determined by extent of cardiac disease.

REFERENCE

1. Adapted from National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents. The fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents. *Pediatrics.* 2004;114(2):555–572

DEFINITION

- Hyperthyroidism is the result of excessive activity of the thyroid gland.
- The clinical manifestation of excessive circulating thyroid hormone is called *thyrotoxicosis*.
  - With a few exceptions, thyrotoxicosis in children is the result of Graves disease.

SIGNS AND SYMPTOMS

- Graves disease often remains undiagnosed for a long time in children because they can continue normal activities without symptoms that are overtly suggestive of hyperthyroidism.
- Clinical signs and symptoms in children who have Graves disease include
  - Goiter
  - Prominence of eyes
  - Exophthalmos
  - Tachycardia
  - Nervousness
  - Increased appetite
  - Weight loss
  - Emotional lability
  - Heat intolerance
  - Frequent stools
- Early nonspecific findings include behavioral findings that largely reflect hyperactivity of the sympathetic nervous system.
  - Nervousness
  - Sleeplessness
  - Emotional lability
  - Decreased school performance
  - Deteriorating handwriting
- More prominent cardiovascular signs include
  - Tachycardia
  - A widened pulse pressure
  - An overactive precordium
- Neuromuscular signs and symptoms include
  - Tremor
  - A shortened deep-tendon reflex relaxation phase
  - Fatigability
  - Proximal muscle weakness
- Despite increased appetite, the child loses weight.
- Symptoms that appear later include
  - Increased perspiration
  - Warmth
  - Heat intolerance
  - Smoothness of skin
- With long-standing disease
  - Tall stature may accompany advanced skeletal maturation in childhood.
  - Curtailment of final height as a result of early closure of the epiphyses does not occur.
- Goiter.
  - Size when first examined varies, and its presence frequently goes unnoticed.
- Thyroid gland.
  - Usually seen as diffusely enlarged.
    - — May be difficult to discern in overweight or obese children
  - Is soft and has a clearly delineated border.
  - Neck examination should include
    - — Palpation for the presence of a thrill
    - — Auscultation for the presence of a bruit
  - Measurement of the size of the lobes and the isthmus is essential in monitoring disease course.
- Eye findings are variable.
  - Severe ophthalmopathy is far less common among children than adults.
  - If present, it is more likely to resolve completely.
  - Findings include
    - — Prominence of the eyes (proptosis or exophthalmos)
    - — A conspicuous stare (caused by lid retraction and a widened palpebral fissure)
    - — Lag of the upper lid on downward gaze

DIFFERENTIAL DIAGNOSIS

- Hashimoto thyroiditis
  - Rarely, children with this disease are
    - — Thyrotoxic
    - — Have a high titer of thyroid-stimulating immunoglobulin (TSI) autoantibodies in addition to antithyroid antibodies
  - The condition has been called *hashitoxicosis*.
  - May be differentiated from routine Graves disease in that the hyperthyroidism is usually a transient phase before progression to permanent hypothyroidism.
- Other causes of hyperthyroxinemia are rare, including
  - Generalized resistance to thyroid hormone that is found in association with attention-deficit/hyperactivity disorder
  - Factitious hyperthyroidism from excessive administration of thyroid hormone
  - Thyrotropin-secreting pituitary adenomas
  - Binding-protein changes characterized by normal free thyroxine (T_4) and thyrotropin levels

- Autonomous thyroid adenomas
  - Can be seen in association with Albright syndrome (precocious puberty, café au lait spots, and polyostotic fibrous dysplasia)

DIAGNOSTIC APPROACH

- Diagnosis of Graves disease rests on demonstrating
  - Elevated levels of T_4
  - Depression of thyrotropin levels to below the lower limit of detectability
- A comparison of the patient's levels and age-appropriate normal values of T_4 must be performed before a diagnosis of hyperthyroidism can be made.

LABORATORY FINDINGS

- Measurement of serum free T_4
  - Should be included in initial assessment.
  - In patients with binding protein increases, total T_4 may be high, yet free T_4 and thyrotropin will be within reference range, thereby ruling out hyperthyroidism.
    - Particularly relevant to women taking oral contraceptives, in whom the estrogen increases the binding protein levels, total T_4, total triiodothyronine (T_3), and thyrotropin concentrations
- Measurement of T_3
  - May help confirm the diagnosis of T_3 toxicosis but is rarely necessary
- In thyrotoxicosis, the response of thyrotropin to thyroid-releasing hormone is blunted severely or absent.
  - Thyroid-releasing hormone stimulation test
    - Necessary only when Graves disease is thought to exist but the diagnosis is unclear.
    - In equivocal situations, measurement of thyroid-receptor antibodies (TRAbs), which are present in 95% of patients who have Graves disease, may help to confirm the diagnosis.
- TSI.
  - In pregnant patients, high levels are predictive of neonatal Graves disease.

DIAGNOSTIC PROCEDURES

- Measurement of thyroid gland uptake of radioiodine or technetium
  - Useful only to distinguish painless thyroiditis from Graves disease
    - Patients who have thyroiditis (hashitoxicosis) have a low uptake.
    - Patients who have Graves disease have a high uptake.
  - Generally not necessary at the time of diagnosis
  - Required if radio-ablative therapy is performed

TREATMENT APPROACH

- Graves disease
  - Optimal long-term therapy continues to be the subject of research and some controversy.
    - Some physicians prefer to titrate the dose of antithyroid medication to maintain the patient in a euthyroid state.
    - Others administer antithyroid medication until the patient's condition becomes hypothyroid and supplement thereafter with thyroid hormone.
    - These varying approaches have no effect on rates of relapse.
  - Therapy with antithyroid medication
    - Usually maintained for a minimum of 18–24 months.
    - During this time, monitoring the size of the thyroid gland and the TRAb levels can be useful.
    - Shrinkage of the thyroid gland and decreasing TRAb titers predict a greater likelihood of remission after discontinuation of therapy.
    - Thereafter, treatment can be stopped, and 20%–40% of patients remain in remission.
  - If a relapse occurs on discontinuation
    - Therapeutic choices include resumption of antithyroid medication or definitive therapy consisting of radioiodine or surgery.
    - With variable consensus, because the rate of sustained remission is lower than the initial rate of remission and because the relative utility of the markers has not been reached, the following features do predict a lower rate of remission:
      - A gland >2.5× normal for age
      - Age <12 years
      - Nonwhite ethnicity
      - Elevated baseline TRAb titer
      - Free T_4 >4 ng/dL
    - The choice depends on factors that affect the chances of success of each form of therapy, such as compliance, patient preference, and surgical expertise.

SPECIFIC TREATMENTS

Antithyroid Medications

- Thioamides
  - Aim of treatment is to reduce thyroid hormone production and block its effect on tissue peripherally.
  - Methimazole is usually used first.
    - Propylthiouracil (PTU) should no longer be used except during the early part of pregnancy.
      - The current recommendation limits its use as a bridge to definitive therapy in the setting of an allergy to methimazole or in early pregnancy.
      - Equally effective in inhibiting thyroid hormone production.
      - However, PTU also blocks the peripheral conversion of T_4 to T_3.
    - The half-life is 3–4 hours for PTU and 6–13 hours for methimazole.
    - Both drugs cross the placenta.
      - PTU does so less than methimazole and, therefore, is the preferred drug during early pregnancy.
    - Both drugs are present in small quantities in human milk.
      - Breastfeeding may be continued.
    - Methimazole induces euthyroidism somewhat faster than PTU and does so within weeks to a few months, depending on the size of the thyroid gland.
  - PTU.
    - Starting doses range from 5–10 mg/kg body weight, with a maximum of 300 mg/d, given in 3–4 divided doses.
  - Methimazole.
    - Dose is ~0.3–0.5 mg/kg, with a maximum of 15 mg/d, given in 2–3 divided doses.
    - Some older adolescents may require >15 mg/d, especially at the start of therapy.
  - Once thyroid hormone secretion is depressed, maintenance doses may be given in 2 or 3 daily doses for PTU and 1 or 2 daily doses for methimazole.
  - Potential side effects
    - Minor reactions that subside spontaneously include a purpuric and papular rash, urticaria, joint pain, stiffness, hair loss, nausea, or headaches.
    - Serious reaction—agranulocytosis.
      - An idiosyncratic reaction that occurs in 1:500–1:1,000 cases.
      - Usually occurs within the first 3 months of therapy after either form of antithyroid medication.
      - Leukocyte count monitoring is not useful in anticipating agranulocytosis because its onset is sudden.
      - Thus, patients need to be told about the significance of a sore throat, mouth sores, and fever as potentially heralding agranulocytosis.
      - Supportive treatment, such as antibiotic therapy and discontinuation of thioamide therapy, are necessary.
      - Spontaneously reverses.
      - Resumption of therapy with a different thioamide does not usually cause recurrence.
    - Such reactions as drug fever, nephritis, hepatitis, or lupus-like reactions are rare.
- Adjuvant β-adrenergic blockade
  - In addition to antithyroid medication.
  - May be accomplished with propranolol to control the sympathetic hyperactivity of severe Graves disease.
    - Therapy is necessary but only transiently.
  - May be contraindicated in patients who have cardiac failure or asthma.
  - Patients at relative risk may better tolerate β_1-selective drugs, such as atenolol.
- Iodide
  - Has a minor short-term role as adjuvant therapy
    - In patients who develop toxicity to PTU or methimazole
    - As adjunctive therapy immediately before thyroidectomy and for treatment of severe thyrotoxicosis
  - In practice, it is seldom used.
  - The American Thyroid Association recommendation is for routine use of supersaturated potassium iodide for attainment of the euthyroid state, with some gland shrinkage and reduced vascularity before thyroidectomy.
  - Works by transient inhibitory effect on iodine organification, leading to a decrease in T_4 and T_3.

Definitive Therapy

- The choice between surgical thyroidectomy and radioactive iodine is a matter of personal preference for many, but not all, patients.
- Surgery
  - Resolves symptoms faster than radioactive iodine therapy (RAI).
  - Permanent hypothyroidism after surgery is frequent.
  - Potential for surgical complications from injury to adjacent structures (recurrent laryngeal nerve damage and hypoparathyroidism) dictates that referral be made to an experienced surgeon.
- RAI.
  - Easy to administer.
  - Safer than surgery and equally efficacious.
  - Patients with very large glands (>80 g) are poor candidates for RAI.
  - Patients with poorly controlled Graves disease (T_4 >20 mcg/dL or free T_4 >5 ng/dL) should undergo RAI with caution because of the risk of thyroid storm.
  - Patients who are pregnant, breastfeeding, or at high risk for pregnancy should not undergo RAI.
  - The role of RAI in children <5 years (who are at the highest risk of thyroid cancer after external radiation) is still under investigation.
  - RAI is being used more extensively in the pediatric population.
    - Fears regarding thyroid carcinoma, leukemia, radiation, and genetic damage after treatment have been alleviated.
    - Radioactive iodine concentrates in the thyroid gland and induces cell death over time.
    - On average, three-quarters of patients are cured after one dose of radioiodine.
    - A small proportion may require a second dose months after the first.

Ophthalmopathy

- Most affected children can be treated with topical ophthalmic lubrication.
- Severe ophthalmopathy.
  - Management can be medical or surgical (eg, orbital decompression, eye muscle or lid surgery).
  - Medical management includes high-dose glucocorticoids or orbital radiotherapy, either alone or in combination.

WHEN TO ADMIT

- Routine diagnosis and therapy of hyperthyroidism do not require hospitalization.
- Some severe complications of the disorder or its therapy (ocular, cardiovascular, infectious) may be managed by appropriate subspecialists and with hospitalization.

WHEN TO REFER

- New diagnosis of hyperthyroidism
- Surgical management

FOLLOW-UP

- Graves disease
  - Continued patient monitoring with thyroid function tests is indicated to detect any subclinical relapse.
  - Following RAI, short-term follow-up care, including thyroid function tests, is required to determine when to institute thyroid hormone replacement, and long-term follow-up care is required as with anyone else on this therapy.

COMPLICATIONS

- Thyrotoxic crisis
  - An exceptional but severe complication.
  - Diagnosis rests on finding uncontrolled hyperthyroidism.
  - Characterized by a constellation of findings, including
    - Cardiac failure
    - Tachycardia
    - Hyperthermia
    - Central nervous system abnormalities, such as confusion, apathy, or coma
  - Infection (even relatively minor) and trauma can be precipitating factors.
  - Therapy must be expeditious and aggressive; should include
    - Antithyroid medication.
    - Iodide.
    - β-Blockade.
    - Antipyresis.
    - Medications to prevent cardiac failure.
    - The initial setting for care should be an intensive care unit, to ensure aggressive control of hyperthermia with ice packs and cooling blankets.
    - Thyroidectomy may be performed after 1 week of iodine, which also reduces the vascularity of the gland and the risk for thyroid storm.

- Neonatal thyrotoxicosis
  - Rare.
  - Due to the transplacental passage of thyroid-directed immunoglobulins from the mother.
    - May occur even if the mother no longer has active thyroid disease.
    - Stimulatory and blocking maternal thyroid antibodies may disappear at different rates, making the course of neonatal Graves disease difficult to predict.
  - Onset may be immediate or delayed for weeks.
  - Duration may be brief or prolonged, lasting up to 6 months.
  - Notably, transient neonatal hypothyroidism may result from the transfer of maternal thyrotropin-binding inhibitory immunoglobulins.
    - May also be caused by suppression of the hypothalamic-pituitary-thyroid axis by placentally transferred maternal T_4 from mothers with hyperthyroidism
  - Clinical signs and symptoms include
    - Microcephaly
    - Frontal bossing
    - Tachycardia
    - Hypertension
    - Irritability
    - Failure to thrive
    - Flushing
    - Exophthalmos
    - Goiter
  - Can also occur
    - Vomiting
    - Diarrhea
    - Hepatosplenomegaly
    - Jaundice
    - Thrombocytopenia
  - Cardiac failure and arrhythmias
    - Account for a mortality rate that approaches 25% when the disease is severe and treated inadequately.
  - Long-term complications are severe and include
    - Hypothyroidism
    - Premature craniosynostosis
    - Intellectual deficits
  - Adjunctive therapy
    - May be necessary until the disease resolves spontaneously, usually within 1–3 months as the maternal antibodies are degraded.
    - In severely hyperactive neonates, propranolol, 2 mg/kg/d, and digitalis for cardiac failure may be required.
    - Glucocorticoid therapy may also be beneficial.

PROGNOSIS

- Graves disease
  - No reliable factors predict the natural course in a given patient, aside possibly from goiter size and severity of disease at onset.
  - The clinical course ranges from progression to overt hypothyroidism on the one hand to progression to thyrotoxic crisis on the other.

Hypocalcemia, Hypercalcemia, and Hypercalciuria

DEFINITION

Hypocalcemia

- Serum calcium level below the age-specific reference range (**Table 1**)

Hypercalcemia

- Serum calcium level above the age-specific reference range (see **Table 1**)

Hypercalciuria

- Excessive renal excretion of calcium, measured as a urinary calcium excretion of >4 mg/kg/d or an elevated calcium to creatinine ratio for age, in a spot or timed urine collection (**Table 2**)
- Most common types of clinically significant hypercalciuria
  - Absorptive
    - Type 1
      - Relatively uncommon.
      - Most severe type.
      - Urinary calcium excretion is relatively unresponsive to dietary modifications, including severe dietary calcium restriction, but can normalize during periods of fasting.
    - Type 2
      - Most common form
      - Responsive to moderate dietary calcium restriction
    - Type 3
      - Relatively uncommon
      - Related to a renal phosphate leak
  - Renal leak
    - Far less common than absorptive form
    - Caused by defects in the kidneys that impair renal calcium reabsorption
  - Resorptive
    - Result of increased osteoclastic bone resorption
  - Renal phosphate leak

PHYSICAL EXAMINATION

Hypocalcemia

- Increased neuromuscular excitability causes hyperreflexia, jitteriness, apnea, paresthesias, laryngospasm, and tetany.
- Older child will have a positive Chvostek sign or Trousseau phenomenon.
- Central nervous system symptoms include
  - Irritability
  - Localized or generalized seizures
  - Fatigue
  - Depression
  - Coma
- Cardiac conduction defects may be observed.

Hypercalcemia

- Signs and symptoms reflect acuity and degree of hypercalcemia and patient age.
- Moderate to severe hypercalcemia affects the nervous system, leading to weakness, hypotonia, lethargy, and seizures.
- Significant polyuria leading to dehydration is produced by stimulation of the calcium-sensing receptor in the renal collecting ducts.
- When severe, nephrocalcinosis, nephrolithiasis, and hematuria may be initial manifestations.
- Gastrointestinal symptoms (anorexia, nausea, vomiting, and abdominal pain) may occur, often accompanied by failure to thrive.
- Cardiovascular signs include hypertension and abnormalities in cardiac conduction.
- In neonates and infants, symptoms are nonspecific and hypercalcemia may be detected in the workup for failure to thrive.

Hypercalciuria

- May present with
  - Dysuria
  - Abdominal or flank pain
  - Nephrolithiasis
  - Recurrent urinary tract infections
  - Osteoporosis
- Physical examination may reveal growth restriction as a manifestation of renal tubular acidosis.
- Symptoms of hypercalcemia may be predominant when hypercalciuria is secondary to hypercalcemic disorder.

LABORATORY EVALUATION

- Reference serum calcium values are age dependent.
- Reference range is broader in infants than older children, and upper limit decreases with age (see **Table 1**).
- To determine the level of active calcium, measure serum concentration of ionized calcium or measure serum total calcium and albumin.

Table 1. Representative Normal Values for Age for Serum Total Calcium Concentration

Age Group	Serum Total Calcium (mg/dL)	
	Male	Female
Newborns and Infants		
0–7 d	7.6–11.3	7.8–11.2
8–30 d	8.8–11.6	8.6–11.8
31–90 d	8.7–11.2	8.2–11.0
91–180 d	8.5–11.3	8.0–11.4
181–365 d	8.0–10.9	8.1–11.0
Children and Adolescents		
1–3 y	8.9–9.9	8.9–9.9
4–11 y	9.0–10.1	9.0–10.1
12–13 y	9.0–10.6	9.0–10.6
14–15 y	9.3–10.7	9.3–10.7
16–19 y	9.0–10.7	9.0–10.7

Modified from Ghoshal AK, Soldin SJ. Evaluation of the Dade Behring Dimension RxL: integrated chemistry system-pediatric reference ranges. *Clin Chim Acta.* 2003;331(1–2):135–146.

Table 2. Spot Urine Calcium to Creatinine Ratio

Age	Ratio
<7 mo	0.07–0.86
7–18 mo	0.07–0.60
18 mo–6 y	0.03–0.42
Adult	0.05–0.22

Derived from Sargent JD, Stukel TA, Kresel J, Klein RZ. Normal values for random urinary calcium to creatinine ratios in infancy. *J Pediatr.* 1993;123(3):393–397.

- A useful formula for estimation of "corrected" total calcium, based on the level of serum calcium, is
  - Adjusted total Ca = measured total Ca + [0.8 × (4.0 – measured albumin)]

Hypocalcemia

- Should include
  - Serum total and ionized calcium
  - Phosphorus
  - Magnesium
  - Parathyroid hormone (PTH)
  - 25-hydroxyvitamin D
- Spot urine calcium and creatinine can be helpful because the calcium to creatinine ratio should be very low in patients with hypocalcemia.
- Measure 25-hydroxyvitamin D (instead of 1,25-hydroxyvitamin D) because it best reflects vitamin D status.
- Patients with hypoparathyroidism have low (or inappropriate) normal serum PTH levels.
- Patients with pseudohypoparathyroidism (PHP) have elevated serum levels of PTH.
  - In both conditions, serum phosphorus levels are elevated.
- Patients with vitamin D deficiency will have elevated serum PTH levels and hypophosphatemia.

Hypercalcemia

- Should include
  - Serum total and ionized calcium
  - Phosphorus
  - Magnesium
  - PTH
  - 25-hydroxyvitamin D
  - Calcitriol
  - Urinary calcium and creatinine
- Hypercalcemia with hypophosphatemia is observed in hyperparathyroidism.
  - Inappropriately elevated PTH level for the calcium level will confirm this diagnosis.
- Familial hypocalciuric or severe neonatal hyperparathyroidism: very low urinary calcium levels with fractional calcium excretion <1%.
- Causes of hypercalcemia with low PTH level include
  - Increased vitamin D intake (elevated serum 25-hydroxyvitamin D)
  - Increased vitamin D activation (elevated serum calcitriol)
  - Malignancy (often with increased PTH-related protein levels)
- Immobilization and calcium gluttony are associated with low serum levels of PTH and vitamin D metabolites but markedly increased urinary calcium excretion.

Hypercalciuria

- Should include
  - 24-hour urine collection
    - Calcium
    - Creatinine
    - Sodium
    - Potassium
    - Citrate
    - Oxalate
  - Serum calcium
    - If elevated, evaluate for hypercalcemia.

IMAGING

Hypocalcemia

- Cerebral calcifications may be observed in chronic hypocalcemia when the calcium-phosphate product has been elevated because of hyperphosphatemia.
  - Long bone radiographs may show demineralization and rachitic changes, such as cupping and fraying of the metaphysis, when hypocalcemia is associated with hypophosphatemia.
    - Most common in patients with vitamin D deficiency or resistance, in whom secondary (adaptive) hyperparathyroidism leads to reduced tubular resorption of phosphorus

Hypercalcemia

- Reserve imaging for confirmation of biochemical diagnosis.
- Renal ultrasound.
  - End-organ damage
  - Nephrocalcinosis or nephrolithiasis
- Radiographs.
  - End-organ damage.
  - Skeletal demineralization or subperiosteal resorption in some cases of primary hyperparathyroidism.
  - Dual-energy x-ray absorptiometry is far more sensitive in demonstrating reduced bone density in most patients with long-standing hypercalcemia.
- Technetium-99m sestamibi scanning and neck ultrasound can identify a solitary parathyroid adenoma in 60%–90% of patients with primary hyperparathyroidism.

Hypercalciuria

- Renal ultrasound may show nephrolithiasis or nephrocalcinosis.
- Computed tomography or intravenous (IV) pyelography may be necessary to clarify questionable obstruction or stones.

SPECIFIC TREATMENT

Hypocalcemia

- Optimal treatment requires vitamin D and oral calcium supplementation.
  - Typical regimen is 20–50 mg/kg of elemental calcium daily in divided doses.
  - Calcium is best taken with meals when the serum phosphorus level is elevated.
- Available calcium salts differ in the amount of elemental calcium per gram of salt.
  - Calcium carbonate (40% calcium).
  - Calcium citrate (21% calcium).
  - Calcium gluconate (9% calcium).
  - With concomitant antacid medication, calcium citrate is preferred.
- Use magnesium supplements when serum magnesium is low.

- Treat vitamin D deficiency with vitamin D.
  - Cholecalciferol (vitamin D_3).
  - Ergocalciferol (vitamin D_2).
  - 1,000–4,000 units per day.
  - Monitor carefully to ensure adequate replacement and to avoid toxicity.
- Patients with chronic hypocalcemia, as in hypoparathyroidism, PHP, or vitamin D–dependent rickets, should be treated with calcium supplements plus calcitriol.
  - 90 ng/kg/d in 2 divided doses.
  - Calcitriol has a much shorter half-life than other forms of vitamin D and does not require PTH action for full biologic effect.
- Patients with acute and symptomatic hypocalcemia require hospital admission and treatment with IV calcium.
  - Injections of calcium salts are recommended only in acute cardiac emergencies.
  - In all other cases of symptomatic hypocalcemia, continuous infusion of calcium, at a rate of 1–3 mg/kg/h of elemental calcium (eg, 10% calcium gluconate), will safely normalize serum calcium levels and maintain constant concentrations better than repeated bolus infusions.
  - Once the serum calcium level has been normalized, the patient can be transitioned to oral therapy with calcium and vitamin D.

Hypercalcemia

- Need for treatment depends on degree of hypercalcemia and presence or absence of clinical symptoms.
  - If calcium levels are <12 mg/dL and patient has no symptoms, treatment of hypercalcemia is usually unnecessary.
  - Children with mild hypercalcemia, Williams syndrome, or vitamin D excess may require nothing more than a low-calcium, low-vitamin D diet.
  - Patients with asymptomatic hypercalcemia caused by familial hypocalciuric hypercalcemia require no intervention.
- Admission.
  - Patients without symptoms may require only adequate hydration.
  - Patients with calcium levels >14 mg/dL should be treated aggressively, regardless of symptoms.
  - Main goals of treatment include
    - Increase urinary calcium excretion.
    - Decrease bone resorption.
  - Aggressive hydration with physiologic (normal) saline solution initially, to induce natriuresis to enhance urinary calcium excretion.
  - Volume expansion using IV saline infusion will increase sodium, calcium, and water delivery to the loop of Henle (ansa nephroni).
    - Consequent marked increase in urinary excretion of calcium as well as sodium, potassium, chloride, magnesium, and water.
  - It is important to replace water, sodium, potassium, and chloride continuously and, if this regimen is >10 hours, to replace magnesium.
    - In older adolescents, urinary flow should be >250 mL/h during this time.
    - Serum calcium level will start decreasing within 2–4 hours and approach reference range in 12–24 hours.
  - In most patients, IV infusion of saline will effect a satisfactory diuresis.
  - Avoid potent loop diuretics or use with extreme caution because they may paradoxically worsen hypercalcemia by inducing dehydration and decreasing the glomerular filtration rate.
  - Parenteral calcitonin and IV bisphosphonates decrease osteoclastic activity and are generally effective in hypercalcemic patients with increased bone resorption.
  - Calcitonin can be given subcutaneously or intramuscularly every 12 hours (4 IU/kg).
    - Rapid action (4–6 hours).
    - Usually decreases calcium level by 1–2 mg/dL.
    - Effective in only 60%–70% of patients.
    - Most patients develop tachyphylaxis in 48–72 hours.
  - IV bisphosphonates
    - Can lower the serum calcium level with a maximal effect in 2–4 days.
    - Duration of effect is 1–4 weeks and varies according to underlying cause and specific bisphosphonate.
    - Zoledronate and pamidronate are the most effective bisphosphonates for treatment of hypercalcemia.
      - Zoledronate
        - Most potent bisphosphonate
        - Longest lasting effect
        - 30-minute IV infusion (up to 4 mg)
      - Pamidronate
        - IV infusion over 4–24 hours.
        - Initial dose varies.

- ► In children with typical renal function, typical dose is 1–2 mg/kg.
  - ◆ Up to 30 mg if calcium level is <12 mg/dL
  - ◆ Up to 60 mg if calcium level is 12–13.5 mg/dL
  - ◆ Up to 90 mg if calcium level is >13.5 mg/dL
- — Subsequent dose of an IV bisphosphonate can be given after 7 days.
- — Bisphosphonates may take several days to reduce the serum calcium level.
- — Combine these agents with rapid-acting therapies (eg, IV saline infusion and calcitonin injections).

- Cause-specific treatment follows initial treatment.
  - — Cinacalcet or surgery in primary hyperparathyroidism
  - — Corticosteroids or ketoconazole, chloroquine, and hydroxychloroquine to inhibit calcitriol production in cases of lymphoma or granulomatous disease

Hypercalciuria

- Management depends on pathophysiology.
- Treat symptomatic hypercalciuria with dietary measures and pharmacotherapy.
  - Increase fluid intake.
  - Reduce daily sodium intake.
- Sodium intake should not exceed the recommended daily allowance.
  - 1.2 g/d for 4- to 8-year-olds
  - 1.5 g/d for 9- to 18-year-olds
- Calcium intake should be maintained at recommended values for age to avoid bone demineralization.
- Primary pharmacologic therapy focuses on reducing urinary excretion of calcium and includes thiazides, orthophosphates, and potassium citrate.
- Other therapies are directed at reducing intestinal absorption of calcium with sodium cellulose phosphate and increased fiber.
- Dipyridamole.
  - Limited success in increasing renal tubular reabsorption of phosphorus and reducing synthesis of 1,25-dihydroxyvitamin D
  - Attractive option in patients with a renal phosphorus leak
- Increased osteoclastic bone resorption (resorptive hypercalciuria) may improve with bisphosphonates.
  - Oral alendronate or IV pamidronate or zoledronate.
  - Increases bone deposition of calcium and, thus, removes it from circulation before it can be excreted.
  - Improves bone density and helps reduce urinary calcium levels.
  - Main benefit may be in protecting bones from calcium depletion and demineralization.
- Potassium citrate.
  - Prevents nephrolithiasis
  - Useful in patients with renal tubular acidosis
  - May prevent lithiasis in patients who are following a ketogenic diet
- In many instances, several drugs will be required to effectively reduce excessive urinary calcium excretion.
- Ultimately, success is limited by factors that reduce compliance over time.
  - Development of medication adverse effects.
    - — Hypokalemia and hypomagnesemia from thiazides
    - — Diarrhea and gastrointestinal distress from phosphate salts
  - Necessity for lifelong treatment.
  - In absence of clinically active stone disease, patients are usually asymptomatic despite significant hypercalciuria and, thus, see no benefit from long-term treatment.

WHEN TO REFER

Hypercalciuria

- Refer children with mild asymptomatic hypercalcemia to outpatient evaluation.
- Refer patients with an active renal stone or history of renal stone for evaluation by a specialist.

WHEN TO ADMIT

Hypocalcemia

- Patients with acute and symptomatic hypocalcemia require hospital admission and treatment with IV calcium.
- Injections of calcium salts are recommended only in acute cardiac emergencies.

Hypercalcemia

- Patients with moderate calcium elevations (12–14 mg/dL) and symptoms consistent with hypercalcemia should be admitted.

Hypercalciuria

- Hypercalciuria per se will not require hospitalization unless there is obstructive stone disease or infection.

FOLLOW-UP

Hypocalcemia

- Chronic hypocalcemia: regular follow-up by an endocrinologist.
- Adjust calcium supplements and vitamin D treatment to maintain calcium levels in the low to normal range to avoid hypercalciuria.
- Maintain the calcium-phosphate product <55 mg/dL/m^2 for several years.
  - Most common in patients with hypoparathyroidism, PHP, and chronic renal insufficiency

Hypercalcemia

- Follow-up depends on the etiology.
- Hyperparathyroidism caused by adenomas: most often from a single adenoma and cured by surgery.
- Other causes may require chronic follow-up to prevent complications.

Hypercalciuria

- Follow-up is scheduled at regular intervals to monitor therapy and complications.

COMPLICATIONS

Hypocalcemia

- Nephrocalcinosis and nephrolithiasis are rare complications.
  - Regularly monitor serum and urine calcium concentrations.
- Use spot urine collections to determine urinary calcium and creatinine concentrations for screening calcium to creatinine ratios.

Hypercalcemia

- Prevent bone disease secondary to increased resorption in hyperparathyroidism by timely resection.
- Manage to prevent or ameliorate secondary renal disease.

Hypercalciuria

- Renal infection or insufficiency secondary to untreated lithiasis

PREVENTION

Hypocalcemia

- Adequate diet and sun exposure to prevent calcium and vitamin D deficiency.
- Recommended daily intake for vitamin D is 400 IU for infants, children, and adolescents.
  - Some children may require higher doses to maintain reference serum levels of 25-hydroxyvitamin D (>32 ng/mL).
- Breastfed infants need to be supplemented with 400 IU of vitamin D per day.
- Recommended calcium intake by age in the United States increases from 210 mg/d at 0–6 months of age to 1,300 mg/d at 9–18 years.

Hypercalcemia

- Etiology-specific and prompt symptomatic treatment to prevent acute hypercalcemia and end-organ damage

Hypercalciuria

- Maintain nutritional and medical treatment in symptomatic patients to prevent recurrent lithiasis.

Hypospadias, Epispadias, and Cryptorchidism

DEFINITION

- Hypospadias and epispadias.
  - External genital deformities.
  - Usually obvious immediately in a male infant.
    - Circumcision should be delayed until a pediatric endocrinologist and a pediatric urologist perform a thorough evaluation.
  - Hypospadias: maldevelopment of the ventral aspect of the penis, urethra, corpora spongiosum and cavernosa, and ventral prepuce.
  - Epispadias: The meatus is formed on the dorsum of the penis at various points along the glans and shaft; on rare occasions, so far back as to be beneath the symphysis pubis.
- Cryptorchidism: undescended testes.
  - Testes are generally descended in a full-term neonate (depending on birth weight).
  - Testes descend from within the abdomen to the scrotum usually by about week 36 of fetal life.
  - Frequently, each testis is of somewhat different size.
  - Retracted penis may seem to disappear (even though it is 4 cm long) in a suprapubic pad of fat; parents should be assured that the condition will correct itself in time.
- Micropenis: rare dysmorphic abnormality in which the penis has a stretched length <2 SDs below the mean, or <2.5 cm in length.
  - Circumcision should be delayed until a pediatric endocrinologist and a pediatric urologist perform a thorough evaluation.

SIGNS AND SYMPTOMS

- Hypospadias.
  - Aberrant meatus at the glans penis, at the sub-coronal margin, or on the corona in ~70% of cases.
  - The remaining cases are characterized by a more proximal meatus located at the mid-shaft, scrotal, or perineal region.
  - Recent schema additionally classify hypospadias as anterior, middle, or posterior on the basis of
    - Location of the meatus after chordee correction
    - Glans (cleft with deep groove and proper clefting, incomplete with split glans and shallow groove, or flat with no groove and short-ending urethral plate at the glans)
    - Quality and width of the urethra
    - Prepuce (incomplete or complete)
    - Degree of penile curvature and presence of scrotal transposition
  - Anterior hypospadias.
    - 65% of cases
    - Glanular or sub-coronal
  - Middle hypospadias.
    - 15% of cases
    - Distal penile, mid-shaft, or proximal penile
  - Posterior hypospadias.
    - 20% of cases
    - Penoscrotal, scrotal, or perineal
  - Pediatricians should attempt to classify during the examination, making note of chordee, meatal stenosis, penoscrotal transposition, and penile torsion.
  - Feeling a bulge or dribbling of urine may indicate a diverticulum.
  - In ~10% of cases, an associated unilateral or bilateral cryptorchidism is present.
  - Severity of hypospadias is best judged at the time of surgery.
- Epispadias.
  - Complete epispadias is the least severe form of exstrophy epispadias complex.
    - Presents with a dorsally open urethral meatus with mild pubic diastasis and a closed anterior abdominal wall and bladder
    - Categorized as glanular, coronal, shaft, or penopubic
  - May be associated with complete urinary incontinence because of involvement of bladder neck area and distortion of the normal architecture of the pubic bones.
  - In most cases, the prepuce is absent at the dorsum of the penis and is redundant tissue hanging from the ventral side, leaving the glans uncovered.
  - The glans is broad and spade-like, with a dorsally directed preputial opening and an upward urinary stream.
  - A dorsal chordee or abnormalities of penile raphe can suggest epispadias in difficult diagnostic cases, such as if the prepuce is covering the urethral defect.

- Cryptorchidism.
  - 75%–80% of undescended testicles are palpable and right-sided.
  - In 10% of boys with undescended testes, testes are nonpalpable.
    - In nonpalpable cases, 50% of the testes are located in the inguinal canal or abdomen, while in 50%, the testis is absent secondary to fetal torsion and infarct.
  - Examine testicular position with neonate in the supine, cross-legged, and standing positions to ensure proper classification and overcome overactive cremasteric reflex.
  - Examiner must feel from above downward, milking the testis from the inguinal canal into the scrotum.
    - Older patients can help this process by coughing or straining.
    - Cold hands and abrupt palpation can invoke the cremasteric reflex.
  - If one or the other testis is not palpable, the examiner should search beyond the scrotum and inguinal canal to the femoral triangle and inner thigh.
  - Undescended testes are associated with inguinal hernia and possibly hydrocele, which can make palpation of the testes more difficult.
  - If the testis is impalpable and a hernia is present, the testis usually lies just inside the internal inguinal ring.
- If undescended, the testes may have stopped descent at some point within the inguinal canal or may still be in the abdomen.
- If a testis has not reached the inguinal canal, the likelihood is greater that it is abnormal.
  - The lower the testis lies in the inguinal canal, the more likely that it is normal.
- Some testes that appear descended at birth may ascend later in childhood.
  - Testicular ascent may account for 2%–20% of all orchiopexies.

DIAGNOSTIC APPROACH

- Hypospadias
  - Severity of the deformity and position of the meatus on the penile under-shaft greatly influence surgical decisions.
  - Any combination of hypospadias and cryptorchidism should be investigated for possible sex development anomaly.
- Cryptorchidism
  - Diagnosis relies on physical examination.
  - Surgical exploration is still the diagnostic standard for diagnosis of nonpalpable testes.

LABORATORY FINDINGS

- Karyotype and hormone analysis
  - May be warranted in patients with undescended testes if there are additional anomalies, which may indicate syndromic cryptorchidism.

IMAGING

- Cryptorchidism
  - Sonography or magnetic resonance imaging may be helpful only with inguinal undescended testis but have low sensitivity for intra-abdominal testes.

DIAGNOSTIC PROCEDURES

- Surgery
  - Used to document the severity of hypospadias
  - Diagnostic standard in cryptorchidism
- Voiding cystourethrogram
  - Only in the patient with hypospadias and an enlarged prostatic utricle
    - Understand the utricle anatomy and assess possible future problems with urinary stasis, infection, stone formation, or difficulty with catheterization.

TREATMENT APPROACH

- Hypospadias
  - Requires surgical correction to create a straight penis, approximate the urethral meatus, normalize voiding and erections, and reconstruct a uniform urethra and glans.
  - Many techniques have similar outcomes.
  - If hypospadias is mild and situated at or close to the corona with relatively little deformity, repair is straightforward.
  - None of the tissue that might be needed for repair should be sacrificed to circumcision.
- Epispadias
  - Surgical repair corrects the dorsal chordee, reconstructs the glans and urethra, and closes the penile skin.

- Cryptorchidism
  - Ambulatory surgery with open orchiopexy for palpable testes or laparoscopic exploration and subsequent orchiopexy for nonpalpable testes is indicated if the testis has not descended by 12 months of age.
    - 2.5- to 8-fold increase in overall risk for malignant transformation of all undescended testes.
    - Early orchiopexy improves chances of fertility.
    - Risk of malignant transformation with orchiopexy increases with age.
    - Controversy exists over whether the noncryptorchid contralateral testis is at increased risk of malignancy.

SPECIFIC TREATMENTS

Hypospadias

- Timing of hypospadias repair depends on
  - The environment in which the patient will be managed.
  - Risk of anesthesia.
  - Penile size.
  - Psychosexual milestones in infancy and early childhood.
  - American Academy of Pediatrics suggests the optimal time for hypospadias repair is 6–12 months of age.
    - Risk of anesthesia >6 months does not differ from that in older patients.
- Surgery is a 1-day, outpatient procedure.
  - Separation anxiety is reduced, allowing surgery earlier in life to minimize potential psychological disruptions caused by genital surgery.
  - 5 steps in hypospadias repair: orthoplasty, urethroplasty, meatoplasty, scrotoplasty, and skin coverage.
    - Can be done in a single stage or multiple stages.
    - 2-stage approach is usually reserved for cases that need a corporoplasty or if there is a paucity of healthy tissue.
    - Outcomes are similar; best technique depends on surgeon experience, meatal position, meatus and glans configuration, presence or absence of chordee, quality of ventral skin coverage, quality of urethral plate, availability of foreskin, and circumcision status.
- Perioperative hormonal therapy is controversial.
  - 5% testosterone cream or intramuscular injections of testosterone propionate can enhance penile size before surgery by inducing better penile vascularization and increasing size of the urethral plate.
  - Several studies have advised androgen stimulation in patients with a small genital tubercle.

Epispadias

- Surgical repair corrects the dorsal chordee, reconstructs the glans and urethra, and closes the penile skin.
- Patients with a pubic diastasis may require pelvic osteotomy for complete repair.
- Circumcision is to be avoided.

Cryptorchidism

- Surgery is performed on an ambulatory basis with open orchiopexy for palpable testes or laparoscopic exploration and subsequent orchiopexy for nonpalpable testes.
- There is no difference in outcomes between open and laparoscopic techniques for nonpalpable testes.
  - The optimal time for surgical correction of cryptorchidism is ~12 months of age.
  - In ipsilateral hernia, with or without hydrocele, herniorrhaphy should be performed to decrease the risk of incarceration postoperatively.
  - 75% of cryptorchid patients have a correct postoperative testicular position.
  - Important to examine for abnormalities periodically.
  - Orchiectomy with prosthesis placement may be performed if the testis is abnormal.
- If parents decline surgery or are reluctant, the potential for descent with a therapeutic trial of human chorionic gonadotropin (hCG) can be explored.
  - hCG 1,500 U/m^2 body surface area intramuscularly twice a week for 4 weeks.
  - hCG has been seen to lead to testicular descent, but success rate is only 10% greater than placebo.
  - Complications are mild with this dosage but include possible reascent, so monitoring is required.
  - If hormonal treatment fails, surgery must be performed.

WHEN TO ADMIT

- All procedures can be done at an ambulatory, same-day surgery center.

WHEN TO REFER

- Refer to pediatric urology.
  - All patients with hypospadias
  - All patients with epispadias
  - Patients with undescended testis or testes at ~1 year of age
- Refer to pediatric endocrinology.
  - Patients with undescended testis or testes and parents who request hormonal treatment
  - Patients presenting with hypospadias or cryptorchidism and genital abnormality

FOLLOW-UP

- Because incidence of cancer is high in undescended testis/testes, even after orchiopexy, individuals who have undergone orchiopexy should be followed carefully.

PROGNOSIS

- Cryptorchidism
  - Infertility and malignancy is associated with cryptorchid testis.
  - Bilateral cryptorchid testes associated with significant lower fertility.
  - Early orchiopexy may improve fertility.
  - 2.5- to 8-fold increase in malignancy in cryptorchid testis.
  - Early orchiopexy decreases the risk of malignancy.
  - Controversy exists if non-cryptorchid contralateral testis is at increased risk of malignancy.
  - Controversy exists if hCG is a true adjunct therapy for cryptorchidism.

PREVENTION

- Individuals who have undergone orchiopexy should be taught self-examination of the testes and instructed to seek medical attention if any abnormality is detected.

Hypothyroidism

DEFINITION

- Clinical state in which production (or incipient failure of production) of thyroid hormones is insufficient to the extent that it leads to clinical manifestations
- Primary hypothyroidism: insufficient thyroid hormone from failure of thyroid gland
- Secondary hypothyroidism: insufficient production of thyrotropin from pituitary abnormalities
- Tertiary hypothyroidism: insufficient production of thyrotropin from hypothalamic abnormalities

SIGNS AND SYMPTOMS

- Hypothyroidism can affect many different organ systems to varying degrees.
- Many of the symptoms and signs of hypothyroidism are different during infancy compared with childhood.

Congenital Hypothyroidism

- During the first month of life, affected neonates may have no clinical symptoms or signs of hypothyroidism.
- In neonates with no functioning thyroid tissue, clinical signs and symptoms rarely present at birth.
  - Almost always present by 6 weeks of age
- Decreased stooling (<1 stool per day).
- Prolonged hyperbilirubinemia (bilirubin level >10 mg/dL >3 days).
- Respiratory distress in a term neonate.
- Birth weight >4,000 g.
- Feeding problems.
- Sleepiness.
- Hoarse cry.
- Facial edema.
- Large posterior fontanel (>0.5 cm).
- Rectal temperature <35°C (95°F).
- Umbilical hernia.
- Macroglossia.
- Bradycardia (pulse <100 beats/min).
- Lethargy.
- Cutaneous mottling, vasomotor instability.
- Hirsute forehead.
- Milder forms of congenital hypothyroidism may be missed by newborn screening programs.
  - Symptoms do not appear until childhood.
  - Children with these milder symptoms usually have
    - Familial goitrous hypothyroidism (dyshormonogenesis)
    - Thyroid dysgenesis: ectopic thyroid gland located somewhere between the foramen cecum of tongue and anterior mediastinum

Acquired Juvenile Hypothyroidism

- Clinical symptoms and signs of older children with hypothyroidism may be nonspecific and insidious in development.
- If disease has been present for >6 months, growth deceleration should be evident.
  - Normal thyroid hormone secretion is essential for normal linear growth.
- Most patients who have juvenile hypothyroidism
  - Have thyromegaly or deceleration of growth.
  - Are usually short in stature.
  - Deceleration of linear growth should be identified by the primary care physician who routinely measures height of the patient.
- Frank obesity is uncommon.
  - Reduction in physical activity, if it occurs, is usually less than reduction in caloric intake.
- Growth retardation (<4 cm/y).
- Delayed dental development and tooth eruption.
- Onset of puberty: usually delayed; rarely precocious.
- Menstrual disorders.
- Galactorrhea.
- Constipation.
- Cold intolerance.
- Weight gain.
- Fatigue.
- Delayed bone maturation.
- Short stature.
- Myopathy and muscular hypertrophy.
- Increased skin pigmentation.
- Physical and mental torpor.
- Pale, gray, cool, mottled, thickened, coarse skin.
- Coarse, dry brittle hair.
- Bradycardia.
- Delayed deep-tendon reflexes.

DIFFERENTIAL DIAGNOSIS

- The range of nonspecific symptoms and physical findings associated with hypothyroidism may result in other diagnoses being considered initially.
- In newborns
  - Liver abnormalities, suspected because of prolonged jaundice
- In older children
  - Chronic fatigue in children with depression
  - Delayed growth in children with simple delayed puberty
  - Weight gain in children with exogenous obesity

DIAGNOSTIC APPROACH

- Most newborns with congenital hypothyroidism will not be diagnosed on the basis of clinical suspicion but via newborn screening programs.
  - Neonates are identified via a newborn hypothyroidism detection program using a dried blood spot collected in the first 24–48 hours of life.
    - Analyzed at a central laboratory
  - In most programs, thyrotropin levels are determined
    - For all neonates
    - For neonates whose total thyroxine (T_4) level falls below a threshold value
  - Neonates identified in these programs must have confirmatory laboratory measurements of free T_4 and thyrotropin performed as soon as possible.
- Thyroid function tests: The most useful tests are usually
  - Serum thyrotropin.
  - Free T_4.
    - Has widely supplanted the determination of total T_4
      - Total T_4 values are significantly influenced by circulating protein concentrations.
      - Less clinically useful.
  - Tests other than serum T_4 and thyrotropin determinations are not usually required in children with suspected hypothyroidism.
- Varying clinical manifestations of disease make diagnosing congenital hypothyroidism on clinical grounds difficult.
  - Some non-hypothyroid neonates may have clinical features suggestive of hypothyroidism but normal thyroid study results.
  - Others may have minimal clinical features, such as
    - Mild periorbital edema
    - Enlarged posterior fontanel
    - Decreased stooling
    - Abdominal distention
  - Children with advanced hypothyroidism and myxedema are usually
    - Chubby
    - Have periorbital edema
- Physical examination.
  - Inspection and palpation of the anterior cervical area enables the examiner to identify an enlarged thyroid gland, even in a neonate.
  - Easiest method for examining thyroid gland of a neonate.
    - Place the neonate in the supine position with the neck hyperextended over the edge of examining table.
    - Feel for the isthmus of the thyroid, just below the hyoid bone.
    - After identifying the isthmus, palpate laterally to delineate the lobes.
    - Lobes are difficult to define in a healthy neonate.
  - Thyroid examination of an older child is easier.
    - The thyroid rises during swallowing.
    - Having the patient swallow water will facilitate identification and delineation of both thyroid lobes as distinct from adjacent tissue.

LABORATORY FINDINGS

- Identification of primary hypothyroidism
  - The combination of a low serum T_4 value and elevated thyrotropin value is diagnostic.
  - A normal free T_4 level and elevated thyrotropin level indicates mild hypothyroidism.
  - Elevation of the serum thyrotropin value is the most sensitive test.
  - Free T_4 determination by direct dialysis is the most accurate method.
    - Least likely to give false-positive or false-negative results from interfering drugs or other substances in serum
- Hypothalamic or pituitary hypothyroidism
  - Low free T_4 and thyrotropin levels are strongly suggestive and should prompt further evaluation.
- Thyroid-binding protein deficiency
  - A benign condition
  - Male patients with normal free T_4 and thyrotropin levels but low total T_4 levels
- Occasionally, a child or infant with coexisting and severe illness may have non-thyroidal illness syndrome (euthyroid sick syndrome), in which
  - The free T_4 level may be low.
  - Low serum triiodothyronine
  - Normal thyrotropin
  - Borderline or frankly elevated reverse triiodothyronine levels
- Autoimmune thyroiditis
  - Elevated serum thyroid peroxidase or thyroglobulin antibodies confirms a presumptive diagnosis.

IMAGING

- Congenital hypothyroidism.
  - Some experts suggest use of radioisotope studies for all neonates with suspected hypothyroidism; others do not.
  - Thyroid scan is listed as optional in the most recent American Academy of Pediatrics (AAP) policy.
  - If thyroid scan is performed
    - Iodine-123 or technetium-99m should be used.
    - Do not use iodine-131, which exposes neonatal thyroid to higher radiation doses.
  - Thyroid scan will distinguish sporadic disease, such as thyroid dysgenesis, from familial goitrous thyroid dyshormonogenesis.
    - Important distinction for genetic counseling.
    - With dysgenesis, the scan will be consistent with agenesis and atopic thyroid tissue.
    - In familial dyshormonogenesis, a normally sized or enlarged thyroid gland will be found in the normal anterior cervical location of the neck.
- Acquired juvenile hypothyroidism.
  - Radioisotope studies are rarely needed.
  - Thyroid uptake studies are indicated when the patient has
    - Diffuse thyromegaly
    - Biochemical evidence of hypothyroidism not caused by autoimmune thyroiditis or goitrogen ingestion
  - It may be necessary to do an ultrasound or scan in case a nodule is felt.
  - In these cases, biopsy or excision biopsy may be necessary to rule out any neoplasm.
- Assessment of skeletal maturation can provide additional data on the duration of hypothyroidism.
  - Not essential.
  - Bone age determination consistent with that of a healthy newborn suggests
    - Recently acquired, mild congenital hypothyroidism
  - Indications that the fetus was affected by hypothyroidism during third trimester are
    - Absence of ossification centers at the knee
    - Presence of only 2 ossification centers in the foot
  - In children, significantly delayed bone age indicates long-standing and severe hypothyroidism.

TREATMENT APPROACH

- The treatment of choice for hypothyroidism in infancy and childhood is daily administration of oral L-thyroxine.
  - Dosage
    - Full term: 50 mcg/d; 10–15 mcg/kg/d
    - <6 months: 25–50 mcg/d; 8–10 mcg/kg/d
    - 6–12 months: 50–75 mcg/d; 6–8 mcg/kg/d
    - 1–5 years: 75–100 mcg/d; 5–6 mcg/kg/d
    - 6–12 years: 100–125 mcg/d; 4–5 mcg/kg/d
    - >12 years: 100–200 mcg/d; 2–3 mcg/kg/d
- Transient hypothyroidism can persist for several weeks or months.
  - The infant requires thyroxine therapy until the antibodies disappear.
- The following factors may interfere with absorption of L-thyroxine and should be avoided when possible:
  - Soy formula
  - Iron
  - Calcium
  - High-fiber foods
- Iodine-containing medications should not be applied to the skin or mucous membranes of neonates for more than a few days.
  - Easily absorbed
  - Block the neonate's thyroid gland

SPECIFIC TREATMENTS

Congenital Hypothyroidism

- The initial dose of L-thyroxine in a term neonate is 50 mcg/d for the first 1–2 weeks.
  - Should be started promptly at initial visit when
    - Screening test results are outside reference range.
    - Serum samples have been sent for confirmatory tests.
    - A scan is abnormal.
  - Clinical studies have indicated that rapid normalization of serum free T_4 and thyroid-stimulating hormone levels with initial L-thyroxine dosing of 50 mcg/d is associated with better long-term development outcomes than using 37.5 mcg/d initially.
  - Neonates with hypothalamic or pituitary hypothyroidism generally have milder hypothyroidism.
    - Should be given 25 mcg/d

- At the end of the second to fourth week, determine that the amount of L-thyroxine is adequate but not excessive by measuring
  - Serum T_4
  - Thyrotropin
- After 1 or 2 weeks
  - 50-mcg/d dose may need to be reduced to 37.5 g/d (or, infrequently, to 25 mcg/d) if
    - Clinical symptoms of hyperthyroidism develop.
    - The serum T_4 value exceeds 16 mcg/dL.
- In athyreotic neonates who have low T_4 values, usually 50 mcg/d is adequate.
- Therapy should be adjusted to maintain serum T_4 levels during infancy in the upper half of the age-adjusted normal range.
  - Optimizes developmental outcome
- Occasionally, the thyrotropin value will not return to normal, even if the T_4 dose is excessive and causes clinical thyrotoxicosis.
  - These neonates may have an abnormality in the feedback set point of thyrotropin secretion.
  - Goal of therapy should be to maintain
    - Normal serum T_4 values
    - Clinical euthyroidism
- Discontinuing L-thyroxine therapy sometime after 3 years of age is a way of testing for transient congenital hypothyroidism.
  - Serum T_4 and thyrotropin levels are determined 2–4 weeks later.
- A trial of no therapy is not necessary for patients documented to have
  - Thyroid aplasia
  - Ectopic thyroid dysgenesis
  - Elevated thyrotropin values after the initial period of therapy

Acquired Juvenile Hypothyroidism

- Older children with hypothyroidism do not share the same urgent need to achieve a euthyroid state.
- Patients who have had a recent onset of mild hypothyroidism may be given a full replacement dose of L-thyroxine.
  - Children ≥3 years with chronic hypothyroidism and clinical symptoms should
    - Be given a low dose.
    - Have the dose gradually increased every 2–4 weeks to the full replacement.
- Rapid correction of hypothyroid state can often be associated with undesirable behavioral side effects.
  - These children act thyrotoxic despite biochemical euthyroidism.
    - Often restless
    - Have a short attention span
    - Emotionally labile
  - A gradual increase in dose seems to minimize problems in adjustment.

WHEN TO ADMIT

- Myxedema coma.
- Parental noncompliance with treatment of a neonate or young infant increases risk for permanent impairment of central nervous system function if thyroid function test results are not maintained in the normal range.

WHEN TO REFER

- Severe congenital hypothyroidism.
- Cause of hypothyroidism not established on initial evaluation.
- Initial therapy does not normalize thyroid function test results within reference range for age.
  - Often not necessarily the reference range provided by the laboratory.
  - The physician must know the reference range of thyroid function test results for age for patient management during the first 2 decades of life.
- Acquired hypothyroidism that is atypical or complex.
  - Disease occurs in infancy or early childhood.
  - Disease is associated with other endocrine or non-endocrine autoimmune diseases.
- When the diagnosis is hypothalamic or pituitary hypothyroidism based on a low free T_4 level (by a method validated in infants and children) and a normal or low thyrotropin level.
  - This form of hypothyroidism is rarely an isolated disease.
  - Association with other hypothalamic-pituitary abnormalities is to be expected.
  - If isolated, genetic evaluation is needed to define cause and potential for recurrence in a family.

FOLLOW-UP

- Congenital hypothyroidism
  - AAP policy for monitoring free T_4 and thyrotropin values
    - <6 months: every 1–2 months
    - 6 months–3 years: every 3–4 months
    - 3 years to completion of growth: every 6–12 months

- Acquired juvenile hypothyroidism
  - Once the patient is receiving a full replacement dose with reference values, adequacy of L-thyroxine therapy is monitored by free T_4 and thyrotropin determinations every 6–12 months.
    - An elevated thyrotropin level, with or without low T_4 value, indicates inadequate therapy or poor compliance; the latter is characterized by variable serum T_4 and thyrotropin values.
      - Levels may be within reference range on one occasion and discordant (normal or elevated T_4 value with elevated thyrotropin value) on subsequent determinations, despite no change in therapy.

COMPLICATIONS

- Congenital hypothyroidism
  - Delays in diagnosis and institution of adequate therapy are usually associated with increased risk of intellectual disability.
  - Neonates with prolonged fetal hypothyroidism have increased risk for impaired intellectual function.
    - Due to maternal hypothyroidism during first trimester or other factors that blocked fetal thyroid function throughout pregnancy
  - Neonates born with delayed skeletal maturation and low T_4 values are most likely to have neurocognitive problems.
  - Mild sensorineural hearing impairment may be fairly common.
    - Should be screened to allow for early intervention
- Acquired juvenile hypothyroidism
  - Adolescents with chronic hypothyroidism and severe growth retardation may never achieve full growth potential.
    - In many cases, linear growth response to therapy is not accelerated.
      - Height percentile achieved as an adult is lower than that predicted by patient's growth before development of hypothyroidism.

PROGNOSIS

- Congenital hypothyroidism
  - Most infants treated adequately since the first month of age have an excellent prognosis for normal intellectual function and linear growth.
- Acquired juvenile hypothyroidism
  - No permanent intellectual impairment is found among patients with juvenile hypothyroidism.
  - Early diagnosis will prevent
    - Development of long-standing hypothyroidism
    - Cessation of linear growth
    - Risk of a decrease in final adult height

Hypotonia

DEFINITION

- Hypotonia indicates diminished resistance to passive movement around the range of motion of a joint.
  - Not a diagnosis in itself
- "Floppy" is a commonly used term that refers to hypotonia or weakness, or both.

HISTORY

- Determine onset of hypotonia.
  - Review birth and perinatal history, including
    - Maternal history, birth records
      - Breech presentation is common in neonates with a subsequently diagnosed motor unit disorder.
    - Perinatal drug administration
    - If preterm, factors surrounding preterm birth
    - Newborn screening results
  - If the child is the parents' first, they may be less likely to recognize an abnormality.
- Determine the character of hypotonia.
  - Is hypotonia improving or worsening?
  - Is weakness intermittent or constant?
  - What is the predominant distribution of weakness: proximal, distal, or global?
  - Photographs or videos can be used to document findings outside the office setting.
- Medical history.
  - Previous infections
  - History of trauma
  - Results of imaging studies
  - Medication history
- Review of systems, including
  - Feeding difficulties
  - Recent history of constipation
- Family history.
  - Construct a pedigree, noting genetic conditions and individuals with weakness or stiffness.
- Developmental history.
  - Include a chronology of developmental milestones.
  - Assess the child's current function and behavior.

PHYSICAL EXAMINATION

- It may be difficult to quantify hypotonia.
  - No readily administered, accurate test exists.
  - Tone may vary greatly during the day or even during the examination.
  - Difficult to determine true strength of infants and young children.
- Examining other family members may help to make the diagnosis.
  - For example, myotonia in the mother of a newborn with suspected myotonic dystrophy
- Observation.
  - Infants and toddlers
    - Apparent mental status (Does the infant appear obtunded?)
    - Sound of cry (eg, cri du chat syndrome)
    - Facial expressions (including assessing for ptosis)
    - Head control, ability to sit
    - Respirations (normal or paradoxical)
    - Mobility (rolling over, crawling, walking)
    - Ability to stand
    - Strength of kicking and pushing movements
    - Bulkiness of musculature
    - Functional testing
  - Children and adolescents
    - Posture
    - Gower sign
    - Mobility
- Perform a full neurologic examination, including
  - Cranial nerve testing
    - Facial and extraocular muscles
      - If weak, the child may sleep with eyelids partly open.
      - Facial muscle weakness may be consistent with congenital myopathies and facioscapulohumeral muscular dystrophy.
    - Tongue (looking for fasciculations or atrophy)
      - Assess with the tongue not protruded.
      - The child should not be crying.
  - Strength assessment
    - Manual muscle group testing
      - Generally cannot be accomplished reliably in children <5 years.
      - Note whether there is slowed muscle relaxation after contraction (myotonia).
  - Tone assessment
    - In infants, an inability to be held upright and suspended in air without slipping through may indicate poor proximal tone.
    - Decreased tone may be difficult to distinguish from diminished strength.
  - Reflexes
    - Deep-tendon reflexes
      - Present or hyperreflexic with central (upper motor neuron) lesions

- Reduced or absent in peripheral (lower motor neuron) lesions/motor unit disorders
- Extensor plantar responses
- Gait
- Hearing assessment

- Examine the skin.
  - Level of jaundice in newborns and infants
  - Signs of trauma (including abusive head trauma)
- Examine carefully for clinical findings consistent with genetic conditions.
  - Down syndrome.
  - Prader-Willi syndrome.
  - High-arched palate and dental malocclusion are observed in some congenital myopathies (eg, nemaline myopathy).
  - An enlarged heart and congestive heart failure may be observed with glycogen storage disease.
- Skeletal features.
  - Joint abnormalities are common.
  - Scoliosis is common.

DIFFERENTIAL DIAGNOSIS

- Focus on diagnosis of the underlying condition.
  - The clinician should conduct a thorough search for systemic disorders.
  - In many instances, a specific diagnosis cannot be made.
- Central hypotonia (brain disorders or dysgenesis).
  - Hypoxic-ischemic encephalopathy
  - Intracranial hemorrhage
  - Infection
  - Metabolic disorders
    - Hyperkalemic periodic paralysis (rare autosomal-dominant disorder with onset usually in infancy or early childhood)
  - Trauma (including abusive head trauma)
  - Hypoglycemia
  - Hypothyroidism
  - Hyperbilirubinemia
  - Chromosomal abnormalities (Down syndrome, Prader-Willi syndrome, cri du chat syndrome)
- Spinal cord injury.
  - May be a complication of breech deliveries
- Anterior horn cell disorders.
  - Spinal muscular atrophy
    - Autosomal recessive with mutation of *SMN* gene at 5q locus.
    - Weakness and muscle wasting are more proximal than distal, more pronounced in legs than arms.
    - Tongue fasciculations.
    - Normal cognition.
    - Type I: onset birth–6 months.
      - Striking paucity of spontaneous movement
      - Never sit independently, even when placed
      - Paradoxical respiration (Chest wall moves inward during inspiration instead of expanding.)
      - Early demise (often by 2 years)
    - Type II: onset 6–18 months.
      - Can sit when placed
      - Survival into adulthood
    - Type III: onset >18 months
      - Weakness after having learned to walk
      - Normal life expectancy
  - Poliovirus infection
- Peripheral nerve disorders.
  - Rare in infancy and very early childhood
  - Most frequently caused by hereditary sensorimotor neuropathies: Charcot-Marie-Tooth disease and variants
    - Gait abnormalities, with Achilles deep tendon reflexes diminished or absent
  - Demyelinating neuropathy (eg, leukodystrophies)
    - Severe weakness, hypotonia, and areflexia
- Neuromuscular junction disorders.
  - Passively acquired autoimmune myasthenia gravis (transient neonatal myasthenia)
    - Perinatal transmission of antibodies from affected seropositive mother.
    - Few patients are symptomatic, and symptoms are usually mild.
    - Weakness is unlikely to develop if it is not present by 1 week of age.
  - Acquired autoimmune myasthenia gravis (juvenile myasthenia)
    - Major features include fatigability and fluctuating weakness, sometimes with generalized hypotonicity and weakness of the limbs.
    - In young children, the onset can be fulminant.
  - Non-autoimmune myasthenic syndromes
    - Patients are seronegative.
    - Some cases are genetic, but testing is not yet generally available.
  - Infantile botulism
    - Rapid onset, usually around age 3 months
    - Constipation; followed by weakness, hypotonia, poor feeding, and diminished activity
  - Medications (eg, magnesium, aminoglycosides)

- Myopathies.
  - Diverse group of genetic, inflammatory, and metabolic disorders; may exhibit multisystem (muscle, brain, heart) involvement
  - Congenital myopathies (frequently hereditary)
    - Early in life, children will have varying degrees of hypotonia, weakness, and respiratory/feeding difficulties.
  - Myotonic dystrophies
    - Infantile form
      - Autosomal dominant and virtually always transmitted by the mother.
      - Hypotonia can be severe at birth and may be associated with poor suck and swallow, weak facial muscles, club feet, and areflexia.
      - But myotonia will not be present clinically or electrically until patients are >5 years.
      - With appropriate support, affected neonates who survive gain strength and tone with time and will walk.
      - If suspected in neonatal period, examine mother for characteristic features of the disorder.
    - Childhood form
      - An autosomal-dominant trinucleotide repeat disorder with locus at 19q13 that can be transmitted by either parent
      - Correlation between severity and the number of repeats
  - Muscular dystrophies
    - Duchenne muscular dystrophy (common)
      - Condition is progressive; patients do not have hypotonia in infancy.
    - Becker muscular dystrophy
      - Later in onset and slower in progression than Duchenne
    - Nemaline myopathy
      - Associated with weakness and hypotonia, sometimes with respiratory and sucking problems early in life
    - X-linked myotubular myopathy
      - Very early onset, with extraocular and facial weakness in addition to more generalized weakness and hypotonia
    - Central core disease
      - Associated with congenital hip dislocation and malignant hyperpyrexia
    - Merosin-deficient type
      - Associated with intellectual disability, seizures, and white matter abnormalities
    - Fukuyama-type congenital muscular dystrophy (Japan)
      - Associated with severe central nervous system (CNS) abnormalities
    - Facioscapulohumeral muscular dystrophy
      - Usually occurs in older children but may present earlier with facial weakness
      - Genetically linked to high-frequency hearing loss
  - Glycogen storage disease type II (Pompe disease)
    - Acid maltase deficiency
    - May be associated with weakness, marked cardiomegaly/congestive heart failure, hepatosplenomegaly
  - Mitochondrial encephalomyopathies
    - May exhibit CNS and muscle involvement; may have increased serum lactic acid levels
- Benign conditions.
  - Benign congenital hypotonia
    - Diagnosis of exclusion
    - Hypotonia with early onset, usually without weakness or developmental delay
    - Frequently associated with joint hyper-laxity, which may lead to dislocations when an adult
- Other conditions that may mimic hypotonia.
  - Ehlers-Danlos syndrome
    - Hyper-laxity of joints simulates hypotonicity.
  - Inflammatory myopathies (dermatomyositis)
    - Rare in very young children.
    - Produce weakness, not hypotonia.

LABORATORY EVALUATION

- Laboratory studies may be selected on the basis of the likely cause of hypotonia.
- Central hypotonia.
  - If considering infection, consider complete blood cell count and viral, urine, blood, and cerebrospinal fluid cultures.
  - Consider fractionated bilirubin in a severely jaundiced infant.
  - Consider serum glucose measurement.
  - Consider electrolyte measurement if hyperkalemic periodic paralysis is suspected.
  - Serum thyroid studies
    - Consider if diagnosis is not obvious on physical examination.
    - Neonatal screening generally includes a test for hypothyroidism.
    - Hyperthyroidism or hypothyroidism may be associated with acquired autoimmune myasthenia gravis.
  - Consider genetic studies (see later in section).

- Anterior horn cell disorders.
  - Consider genetic studies (see later in section).
  - Consider stool culture for poliovirus.
- Peripheral nerve disorders.
  - Consider genetic studies (see later in section).
- Neuromuscular junction disorders.
  - Acetylcholine receptor antibody test
    - Can be used to confirm diagnosis of acquired autoimmune myasthenia gravis, when, after edrophonium test, abnormal findings subside
    - May not be positive in milder cases
    - Less useful in children than in older individuals
    - Negative in patients with non-autoimmune myasthenic syndromes (eg, congenital myasthenia gravis)
  - Botulism studies
    - Stool analysis: *Clostridium botulinum* or botulinum toxin confirms the diagnosis.
    - Cell culture: Isolation of *C botulinum* confirms the diagnosis.
  - Consider magnesium levels and therapeutic drug monitoring (aminoglycosides).
- Myopathies.
  - Serum creatine kinase levels
    - Markedly elevated in
      - Duchenne muscular dystrophy
      - Becker muscular dystrophy
    - Not always increased in congenital myopathies
    - Generally normal or only minimally increased in spinal muscular atrophy
  - Serum lactic acid
    - May be elevated in mitochondrial disorders
  - In setting of hepatomegaly (as can be seen in glycogen storage disease)
    - Consider liver enzymes (aspartate aminotransferase, alanine aminotransferase), liver function tests (prothrombin time, international normalized ratio, partial thromboplastin time, albumin, protein), and ammonia level.
- Genetic studies.
  - May confirm genetic disorder suspected on clinical grounds, sparing patient from painful studies when conclusive
  - Consider karyotype and specific studies for
    - Spinal muscular atrophy
    - Myotonic dystrophy
    - Some hereditary sensorimotor neuropathies (demyelinating and X-linked)
    - Some mitochondrial myopathies
    - Duchenne muscular dystrophy
    - Becker muscular dystrophy
    - Hypo-myelinating neuropathy
    - Facioscapulohumeral muscular dystrophy
    - Myasthenic syndromes
    - Cri du chat syndrome
    - Prader-Willi syndrome

IMAGING

- Imaging may be used to examine the CNS or musculature.
- Imaging modalities include
  - Magnetic resonance imaging or computed tomography
    - Brain scan may reveal a lesion.
    - May be used to assess muscle mass.
    - Indicated if muscle biopsy is contemplated in a patient with very small muscles.
  - Ultrasonography
    - May be used to assess muscle mass
    - Indicated if muscle biopsy is contemplated in a patient with very small muscles
  - Chest radiograph
    - May be used to assess thymic size in acquired autoimmune myasthenia gravis
- May consider additional focused studies depending on clinical picture (eg, echocardiography in case of cardiomyopathy).

DIAGNOSTIC PROCEDURES

- Procedures may be selected on the basis of the likely cause of hypotonia.
- Sometimes the diagnostic yield of procedures may be higher for other family members.
- Electromyographic studies may be abnormal for neuropathies or myopathies, with differing characteristic findings.
- Peripheral nerve disorders.
  - Nerve conduction studies.
    - May help to distinguish between axonal and demyelinating neuropathies
    - Nerve conduction is extremely abnormal in hypo-myelinating neuropathy.
  - Nerve biopsy is diagnostic for hypo-myelinating neuropathy.
- Neuromuscular junction disorders.
  - Repetitive stimulation studies
    - Helpful in diagnosing disorders of the myoneural junction (eg, infantile botulism)
    - Can be quite painful

- Myopathies.
  - Muscle biopsy

TREATMENT APPROACH

- Treatment varies according to the underlying condition.

SPECIFIC TREATMENT

- For most causes of hypotonia, treatment is supportive.
- A multidisciplinary team may coordinate interventions.
- For spinal muscular atrophy, consider
  - Physical therapy
  - Respiratory therapy
  - Nutritional support as needed
  - Genetic counseling
  - Scoliosis treatments (eg, body jacket, molded back support, surgery)
  - Motorized wheelchair for children with type II at ~2–3 years of age.
- For children with peripheral nerve disorders, consider
  - Bracing for foot drop
- For children with neuromuscular junction disorders
  - Hospitalization, with respiratory and nutritional support as needed
  - Passively acquired autoimmune myasthenia gravis (transient neonatal myasthenia)
    - Give pyridostigmine until asymptomatic, then taper over 1–2 weeks.
  - Acquired autoimmune myasthenia gravis (juvenile myasthenia)
    - Consider anticholinesterase drugs, immunosuppressive treatment, intravenous γ-globulin, corticosteroids, or thymectomy.
  - Non-autoimmune myasthenic syndromes (congenital myasthenia gravis)
    - Consider anticholinesterase inhibitors, corticosteroids, or diaminopyridine (experimental).
  - Infantile botulism
    - Anti-botulism immune globulin may be therapeutic.
- For children with myopathies
  - Infantile form of myotonic dystrophy–type hypotonia
    - Assisted ventilation as indicated.
    - Consider gastrostomy tube feedings.
  - Glycogen storage disease
    - Consider enzyme replacement therapy.
      - Without therapy, prognosis is dismal.

WHEN TO REFER

- Persistent lack of normal motor development
- Regression of motor development
- Sudden or precipitous worsening of tone or strength
- Swallowing dysfunction
- New onset of neurologic signs

WHEN TO ADMIT

- Inability to maintain adequate oxygenation
- Mental status changes
- Not clinically stable

PROGNOSIS

- Benign congenital hypotonia
  - By 5 years, many affected children are indistinguishable from other children their age.
- Spinal muscular atrophy
  - Type I: progressive, typically with death at age <2 years
  - Type II: life expectancy into the 20s or later
  - Type III: normal life expectancy
- Myopathies
  - Infantile form of myotonic dystrophy–type hypotonia
    - A neonate who survives will gain strength and tone and will eventually walk.
  - Myotonic dystrophy
    - Severity correlates with the number of trinucleotide repeats.
  - Glycogen storage disease
    - Prognosis is dismal without enzyme replacement therapy.

PREVENTION

- Genetic counseling
- Prenatal diagnosis

Immune Thrombocytopenia Purpura

DEFINITION

- Immune thrombocytopenia purpura (ITP) of childhood is an acquired immune-mediated, and usually self-limiting, condition of low platelet counts.
- Persistent ITP refers to ITP lasting between 3 and 12 months from diagnosis, which includes
  - Patients not achieving spontaneous remission *or*
  - Patients not maintaining their response after stopping treatment between 3 and 12 months from diagnosis
- Chronic ITP is reserved for patients with ITP lasting >6 months.

SIGNS AND SYMPTOMS

- Typically, there is sudden onset of petechiae, purpura, and ecchymosis in the absence of other signs of illness.
- Mucosal (nose, mouth, and gingival surfaces) bleeding may be present.
- The Intercontinental Cooperative ITP Study Group conducted a prospective registry defining severe hemorrhage at diagnosis and during the following 28 days in children with ITP.
  - Of 863 patients evaluated for bleeding severity at diagnosis and during the subsequent 4 weeks
    - 2.9% had severe bleeding at diagnosis.
    - 0.6% had new severe hemorrhagic events during the ensuing 28 days, suggesting that severe bleeding is rare over the first month.
- Usually, there are no significant abnormalities on history and physical examination.
  - No other systemic symptoms, such as fever, weight loss, bone pain, or joint pain.
  - No significant enlargement of lymph nodes, liver, or spleen.
  - If any of these symptoms or physical findings is present, the case is not typical of ITP and other diagnoses should be considered.

DIFFERENTIAL DIAGNOSIS

- Infections such as Epstein-Barr virus, hepatitis C, and HIV can be ruled out by
  - History
  - Physical examination
  - Liver enzymes/function tests and viral studies, if needed
- Drugs such as heparin and sulfonamides can be ruled out by history.
- Other autoimmune diseases, such as systemic lupus erythematosus
  - May be difficult to diagnose.
  - Are more likely to affect teenagers and adults than younger children.
  - Common variable immunodeficiency and autoimmune lymphoproliferative syndrome should be considered in cases of multiple autoimmune cytopenias.
- Acute leukemia or bone marrow failure.
  - Children with leukemia usually have symptoms and abnormal physical findings not seen in ITP.
    - Hepatosplenomegaly
    - Lymphadenopathy
    - Leukocytosis (white blood cell count >10,000/mcL)
    - Significant anemia (hemoglobin count <10/dL)
- Acquired aplastic anemia.
  - Low platelet count is usually associated with other significant changes in peripheral blood, such as
    - Macrocytic anemia
    - Leukopenia
    - Neutropenia
- Destructive thrombocytopenias, such as thrombotic thrombocytopenic purpura and disseminated intravascular coagulation (DIC).
  - Patients with these conditions present with other clinical and laboratory abnormalities and are usually sicker than ITP patients.
- Inherited thrombocytopenia.
  - Although thrombocytopenia in most children is autoimmune or drug related, keep this category in mind.
  - Elicit a family history of thrombocytopenia, especially parent-child or maternal uncle–nephew.
  - Diagnostic features on peripheral smear that may point to inherited thrombocytopenia include
    - Abnormal size of platelets (small or giant)
    - Absence of platelet α-granules (gray platelets)
    - Döhle-like bodies
    - Microcytosis
  - Clinical features that suggest inherited thrombocytopenia include
    - Bleeding out of proportion to the platelet count
    - Onset of thrombocytopenia early in life

- Associated features, such as
  - Absent radii
  - Intellectual disability
  - Renal failure
  - High-frequency hearing loss
  - Cataracts
  - History of a stable level of thrombocytopenia for years

- Type 2B von Willebrand disease results in increased spontaneous binding of the high-molecular-weight von Willebrand factor (VWF) multimers to platelets.
  - Can lead to increased clearance of platelets from circulation, resulting in variable thrombocytopenia.
  - Usually of autosomal-dominant inheritance, so important to obtain family history regarding mucocutaneous bleeding.
  - If suspected, VWF studies including multimer analysis should be done in consultation with a hematologist.

DIAGNOSTIC APPROACH

- ITP is a diagnosis of exclusion after considering other causes of isolated thrombocytopenia.
- For a patient with mucocutaneous signs of bleeding who is otherwise healthy, a reasonable workup includes
  - Complete blood cell count
  - Peripheral blood smear
  - Reticulocyte count
  - Blood typing
- Complete blood cell count.
  - Thrombocytopenia is usually the only laboratory abnormality.
  - Platelet count is usually <20,000/mcL.
- Peripheral blood smear.
  - Will reveal morphologically normal leukocytes and erythrocytes.
  - Large, freshly produced platelets are usually seen.
    - These young reticulated platelets contain messenger RNA and are metabolically active.
    - May explain why ITP patients do not bleed as severely as those with bone marrow failure and similarly low platelet counts.
  - If other abnormalities are seen, obtaining additional tests may be indicated, such as
    - Viral antibodies (HIV, cytomegalovirus, Epstein-Barr virus, varicella, rubeola, mumps, or parvovirus, depending on the clinical picture)
    - Tests for rheumatologic and other hematologic conditions (eg, leukemia, bone marrow failure)
- Reticulocyte count.
  - Helpful when diagnosis of ITP is not straightforward (ie, in cases in which associated mild anemia exists, which is not rare)
- Blood typing.
  - For Rh status to determine whether a patient is treatable with anti-D antibodies
- Reticulocyte count and blood typing are not strictly needed for evaluation.
  - However, drawing blood to keep aside for reticulocyte count and blood typing is preferable to performing multiple traumatic blood draws on a thrombocytopenic child.
- Platelet antibodies tests.
  - Although ITP is caused by platelet antibodies, these tests are sensitive but not specific.
  - Not indicated for the diagnosis of acute ITP in children.
- Assessment of bleeding time.
  - Bleeding time is prolonged in ITP, but this test is unnecessary, traumatic, and inaccurate in children.
- Tests for prothrombin time and activated partial thromboplastin time are unnecessary.
  - Results are typically normal in these patients.

DIAGNOSTIC PROCEDURES

- Bone marrow biopsy
  - Performed in the past by many pediatric hematologists to rule out acute lymphocytic leukemia for fear of partially treating and thus masking a leukemic process
  - Now, typically performed when patients have clinical or laboratory features atypical of ITP at presentation that suggest an alternate diagnosis, such as acute leukemia or a bone marrow failure syndrome
  - Also indicated for patients in whom ITP is initially diagnosed but who do not respond to treatment
    - Timing of bone marrow evaluation is an individualized decision.
    - Most likely time is between 7–14 days after treatment begins, but response is poor.
  - May be considered
    - In patients who have an atypical clinical course
    - In patients in whom splenectomy is contemplated for additional confirmation of diagnosis
    - To rule out a malignant process

- Bone marrow in ITP
  - Is cellular, with normal erythroid and myeloid precursors
  - Usually shows increased numbers of megakaryocytes

TREATMENT APPROACH

- Early treatment does not alter the natural course and does not affect the development of chronic ITP.
- The same principles of treatment of acute ITP apply to a certain extent to management of chronic ITP.
- Most ITP cases in children can be managed on an outpatient basis.
- Consensus is that treatment is indicated for the patient with overt bleeding.
  - Treatment and management recommendations for patients who have different clinical manifestations remain a subject of debate.
  - Current therapy recommendations are based on expert consensus opinions.
- American Society of Hematology guidelines.
  - Children with ITP and platelet counts >30,000/mcL
    - Require no treatment if they have few or no symptoms, as is usually the case.
  - Patients with platelet counts between 10,000 and 30,000/mcL
    - Treatment recommendations are based on the presence and severity of associated bleeding symptoms or the risk of bleeding.
    - The lower the platelet count, the more likely the patient is to receive treatment, even if symptoms are relatively mild.
  - Children who should be treated
    - Those with platelet counts <10,000/mcL and purpura.
    - Those with any concomitant or preexisting bleeding disorder.
    - Those with extensive purpura of the mucosal membranes may have a higher bleeding risk and should be treated more often than not.
- Other important factors in treatment decision include
  - Child's age
  - Child's degree of activity
  - Social variables, such as reliability of caregivers and ease of access to emergency medical care
- When therapy is indicated, the primary treatment options for the newly diagnosed patient are
  - Corticosteroids
  - Intravenous immunoglobulin (IVIG)
  - Intravenous anti-D immunoglobulin
- Platelet transfusions.
  - Ineffective because the transfused platelets are rapidly destroyed
- Chronic ITP: The chance of spontaneous remission is still significant during this period, making deferral of more aggressive therapeutic approaches reasonable.
  - Other options include splenectomy, immunosuppressive therapy, rituximab, and thrombopoietin (TPO) receptor agonists.
- General useful advice to families with an affected child includes
  - Avoid activities associated with increased likelihood of trauma, such as contact sports.
  - Make sure the child uses a helmet when riding a bicycle.
  - Avoid medications that interfere with platelet function, such as aspirin and nonsteroidal anti-inflammatory drugs.

SPECIFIC TREATMENTS

Corticosteroids

- Used for many years in all age groups.
- Reduce the risk of symptoms by different mechanisms, most likely by reducing reticuloendothelial system phagocytosis of antibody-coated platelets.
- Most pediatric hematologists use prednisone for 2–3 weeks.
  - Shorter courses at higher doses are also effective.
  - Intravenous or oral methylprednisolone up to 3–7 days and dexamethasone for 4 days every 4 weeks have been given.
- Most patients respond to steroids.
  - Response is faster with higher doses (seen after 72 hours of starting treatment).
  - Platelets usually decrease after steroids are discontinued if the titer of platelet antibodies remains elevated.
- A second course of treatment may be necessary
  - If bleeding develops
  - If the platelet count decreases to <10,000/mcL
- Side effects of brief courses of corticosteroids include
  - Behavioral changes.
  - Sleep disturbance.
  - Increased appetite.
  - Hyperglycemia.
  - Weight gain.

- Side effects are more pronounced at higher doses.
- Caution should be taken when using steroids in the setting of active infection, especially with varicella infection.

IVIG

- Compared with patients receiving steroids
  - Rapid improvement in platelet count is seen, usually within 24 hours.
- Probably interferes with Fc receptor activity, resulting in prolonged survival of antibody-coated platelets
  - Other mechanisms of action include
    - Regulatory properties of anti-idiotypic antibodies in IVIG
    - IVIG effects on cytokine synthesis and on receptors for cytokines and complement
  - One intriguing proposal for mechanism of action
    - Concentration-dependent elimination of immunoglobulin G (IgG) can be found from the plasma and IVIG administration causes acceleration of the rate of IgG catabolism.
      - Such a process would eliminate individual IgG molecules in direct proportion to their relative concentration in plasma.
      - Thus, elimination of antiplatelet antibodies is accelerated.
- Far more expensive than therapy
- Side effects
  - Chills.
  - Fever.
  - Headache.
  - Nausea and vomiting.
  - Tend to be more pronounced in older patients.
  - Neutropenia (absolute neutrophil count <1,500/mcL) develops in ~30% of patients.

Anti-Rho(D) Ig

- Binds to the D-antigen in Rh-positive individuals; the antibody-coated red cells block the Fc receptor of reticuloendothelial cells.
  - Results in rapid increase in platelet count, usually in 1–2 days
- A single dose of 50–75 mcg/kg is most commonly used.
  - Achieves a more rapid increase in platelet count that is similar to that seen with IVIG therapy
- An average decrease in the hemoglobin level of ~1.3 g is seen as a result of the mild hemolysis of the patient's Rho(D)-positive red cells.
  - Should be used with caution in children with preexisting anemia.
  - Should probably be given only to children with a hemoglobin level >10 g/dL.
  - With increased use, there have been a few cases of patients developing increased hemolysis leading to severe anemia, acute renal insufficiency, DIC, and multisystem organ failure.
    - It should always be used with caution.
    - It is recommended that patients treated with anti-Rho(D) receive intravenous fluids and be observed for the development of hematuria and hemoglobinuria for at least 8 hours.
    - Signs and symptoms of intravascular hemolysis include back pain, shaking chills, fever, and discolored urine or hematuria.
      - Absence of the signs and symptoms of intravascular hemolysis within 8 hours does not indicate that intravascular hemolysis cannot occur subsequently.

TPO Receptor Agonists

- A number of studies with TPO receptor agonists have shown encouraging results in adults.
- Some children have been successfully treated, and new information about safety and response is emerging.

WHEN TO ADMIT

- Significant bleeding
- Severe anemia
- Significant concern for possible traumatic injury
- Any neurologic change in the setting of thrombocytopenia

WHEN TO REFER

- History of fever or bone pain
- Hepatomegaly, splenomegaly, significant lymphadenopathy
- Family history of thrombocytopenia
- Platelet count <20,000/mcL
- Abnormal leukocyte count on peripheral smear or associated anemia
- Lack of response to initial therapy
- All children with refractory ITP

FOLLOW-UP

- Patients should have blood counts done once or twice weekly.
- Blood counts should be less frequent when the platelet count is
  - Stable
  - >30,000 cells/mcL
  - Increasing with time

COMPLICATIONS

Intracranial Hemorrhage (ICH)

- ~15%–20% of pediatric patients will develop moderate or major hemorrhagic problems.
- ICH is rare; it occurs in 0.1%–1.0% of acute ITP.
- The most serious complication and most likely cause of death in ITP.
- Recognizing which patients are more likely to develop ICH is difficult.
  - A literature review of 62 reported pediatric and adolescent cases of ICH in the setting of ITP showed
    - Median time from the diagnosis of ITP to ICH was 32 days (range, 0 days–8 years).
    - 72% of cases occurred ≤6 months of diagnosis.
    - Platelet count was <10,000/mcL in 71.4% of the cases.
    - Treatments before the ICH was primarily steroids but also included IVIG, splenectomy, and others.
    - A significant number of patients developed ICH despite having already initiated steroid treatment.
  - Many patients have other risk factors, including
    - Preceding head injury
    - Other preceding mucocutaneous bleeding
    - Prior aspirin treatment
    - Arteriovenous malformations
- Management is an emergency that requires
  - Immediate imaging (computed tomography) to determine location and extent of the bleeding
  - Immediate consultation with
    - Pediatric intensivist
    - Hematologist
    - Neurosurgeon
    - General surgeon
- Treatment includes
  - Administration of IVIG, steroids, continuous platelet transfusions to rapidly increase the platelet count
  - Surgical intervention, if needed, including
    - Craniotomy (especially with posterior fossa hemorrhages that are more likely to cause herniation or brain stem compression)
    - Splenectomy

Immune Thrombocytopenia in the Neonate

- Most neonatal thrombocytopenia is not immune in nature but is caused by
  - Sepsis
  - Congenital infections
  - Drugs
  - Asphyxia
  - Necrotizing enterocolitis
- 2 conditions occur when immune thrombocytopenia is seen in neonates.
  - Neonatal alloimmune thrombocytopenia (NAIT).
    - A condition in which the mother develops antiplatelet antibodies directed against specific antigens found on fetal platelets but lacking on hers.
    - Associated 20% risk of ICH.
    - Treatment usually involves administration of maternal washed platelets and IVIG.
    - Importance of detection and accurate diagnosis of NAIT is in the ability to prevent complications in future pregnancies by
      - Treating the mother with IVIG and steroids
      - Performing in utero blood sampling and intervening in case of thrombocytopenia
    - Hematologist and high-risk fetal-maternal specialist should be involved in management.
  - Another less serious condition is that resulting from passive transfer of maternal platelet autoantibodies in a mother with ITP.
    - Only 4% of babies born to mothers with ITP have platelet counts <20,000/mcL.
    - The risk of ICH is low (<1%), and no proof exists that cesarean delivery alters that risk.
- Usually resolves within a few weeks as the antibodies are used up.
  - Physicians may choose to treat the babies with IVIG in case the platelet count decreases to <30,000/mcL.
  - Maternal ITP is not a contraindication to breastfeeding.

Chronic ITP

- Defined as persistence of thrombocytopenia lasting >6 months from the time of diagnosis.
  - ~10% of patients with typical ITP develop chronic thrombocytopenia.

- In a prospective Dutch study, variables that predicted development of chronic disease included
  - Platelet count >10,000/mcL at the onset.
  - Absence of infection shortly before the onset of the disease.
  - The 232I/T Fc gamma receptor IIB genotype.
  - In another meta-analysis, female gender and older age (>11 years) at presentation, among other variables, correlated with increased likelihood of developing chronic ITP.

- Given sufficient time (even years), a significant proportion of such patients will improve or remit.
  - Management should focus on
    - Minimizing risk for bleeding
    - Maintaining a safe platelet count
    - Many patients will require no treatment
- If treatment is needed
  - Periodic short courses of steroids may be given.
  - In case of long-term need for steroids, alternate-day dosing may be effective in preventing bleeding while reducing side effects.
  - IVIG or anti-Rho(D) immunoglobulin has also been used, but these measures are only temporary.
  - Splenectomy.
    - Effective in improving the platelet count and reducing the associated risk of bleeding in 60%–90% of children.
    - A small but real risk remains of overwhelming postsplenectomy sepsis, which may be life threatening.
      - Usually delayed until the child is >5 years because the risk of overwhelming sepsis decreases with age.
      - American Society of Hematology guidelines recommend waiting until ≥12 months after diagnosis, if possible.
    - Platelet counts following splenectomy.
      - Generally monitored indefinitely.
      - Any drop in platelet counts or increase in symptoms should prompt assessment for the presence of an accessory spleen.
    - If not previously done, bone marrow biopsy is recommended for patients being considered for splenectomy.
    - Pre-splenectomy immunizations and subsequent penicillin prophylaxis are necessary.
  - Rituximab for refractory chronic ITP.
    - A chimeric murine-human anti-CD20 monoclonal antibody.
    - Acts by destroying B lymphocytes by activating complement-dependent and an antibody-dependent cellular toxicity.
      - Therefore, mechanism of action is a slow but effective decrease in production of antibodies.
    - In a study of 24 patients 2–19 years of age who received 375 mg/m^2 of rituximab in 4 weekly doses
      - 63% achieved complete remission for 4–30 months (platelet count >150,000/mcL).
    - Although long-term remissions have been documented, use of rituximab in ITP is relatively recent.
    - Long-term follow-up may be needed for accurate prognostication.
    - Use may be associated with
      - Infusion-related reactions
      - Development of transient hypogammaglobulinemia

PROGNOSIS

- Treatment does not alter the course (ie, the incidence of patients who go on to develop chronic ITP).
  - It does shorten the duration of thrombocytopenia in some patients.
- For typical cases of childhood ITP
  - 80% of patients will have platelet counts return to normal ≤2 months of presentation, with or without therapy.
  - Another 10% will recover normal platelet levels in the next few months.
  - ~10% will go on to have chronic thrombocytopenia (>6 months' duration).
- ~25% of children will have a relapse after initial treatment.
  - 10% have chronic ITP.
  - 10% have recurrence but resolution ≤6 months.
  - 5% have ITP recurrences and remissions throughout their lives.

BACKGROUND

- Vaccination was one of the most important achievements in public health in the 20th century.
- Current US disease levels are 92%–100% lower than in the prevaccination era.
- However, many children in the United States, as well as other countries, still die from vaccine-preventable diseases.

GOALS

- Routine childhood vaccination is one of the few health care interventions that saves lives and dollars.
- Routine vaccination saves $2 (for hepatitis B vaccination) to $29 (for measles-mumps-rubella [MMR] vaccination) for every dollar spent.
- The primary reason for the low disease incidence is high immunization coverage levels.
- The process of vaccinating children and adolescents is becoming increasingly complicated as the number of vaccines and vaccine combination choices increases.
- The current US recommended childhood and adolescent immunization schedule is updated annually.

GENERAL APPROACH

Live Vaccines

- Live vaccines include
  - MMR
  - Varicella
  - Rotavirus
  - Yellow fever
  - Vaccinia (smallpox)
  - Oral polio vaccine (OPV)
  - Bacille Calmette-Guérin
  - Oral typhoid
- Live vaccines replicate in the body.
- Live vaccines should be administered subcutaneously; however, are likely effective if given intramuscularly (IM) and do *not* need to be repeated if given IM.
- Live injected vaccines usually induce immunity through a single dose; however, ≤5% of people will not seroconvert with the first dose, which is why the second dose is recommended for MMR and varicella.
  - Unlike inactivated vaccines, live vaccines are susceptible to vaccine failure caused by circulating antibodies, including residual maternal antibodies in infants, which was more common when mothers had wild-type MMR antibodies than currently with vaccine-induced antibodies.

Inactivated Vaccines

- Inactivated vaccines include
  - Inactivated polio vaccine (IPV)
  - Inactivated influenza vaccine (IIV)
  - Hepatitis A
  - Rabies
  - Acellular pertussis
  - Hepatitis B
  - Human papillomavirus (HPV)
  - Split virus influenza
  - Typhoid Vi
  - Toxoid agents
    - Diphtheria
    - Tetanus
  - Polysaccharides, unconjugated
    - Pneumococcal
    - Meningococcal
  - Polysaccharides, conjugated
    - *Haemophilus influenzae* type b (Hib)
    - Pneumococcal
    - Meningococcal
- Inactivated vaccines
  - Do not contain infectious particles that can replicate in the body.
  - Generally require several doses to immunize patients completely.
  - Should be administered IM.

Timing of Administration

Routine Schedule

- The routine vaccination schedule is harmonized among the
  - American Academy of Pediatrics (AAP)
  - American Academy of Family Physicians (AAFP)
  - Centers for Disease Control and Prevention (CDC) Advisory Committee on Immunization Practices (ACIP)
- The schedule allows for office preferences by indicating acceptable ranges for routine on-time vaccination administration.
- The ranges were created so that offices might accommodate routine vaccination into their health supervision visit schedule.
- To ensure timely immunizations, vaccinating *early* within the acceptable age range is important.
- The current version of the vaccination schedules can be found on the CDC Web site at www.cdc.gov/vaccines/schedules/hcp/child-adolescent.html.
- Intervals between different vaccines.
  - Using all routine vaccines simultaneously is safe and effective, provided that vaccines are not combined within a single syringe.

- No contraindications exist to giving any 2 different routine childhood vaccines at the same visit.
  - The Vaccine Information Statement for IIV does state that young children receiving IIV along with pneumococcal conjugate vaccine (PCV13) and/or diphtheria, tetanus, and acellular pertussis (DTaP) vaccine may be at slightly increased risk of febrile seizure, but this is not a contraindication to giving all 3 together.
- Individual vaccines that are not administered on the same day may be given without regard to intervals, with the exception that
  - Live vaccines (ie, MMR and varicella, but *not* rotavirus) that are not administered on the same day should be separated by at least 4 weeks.
  - The 4-week separation rule is intended to reduce theoretical risk of interference from the first vaccine on the subsequent vaccine.
    - If, for example, varicella vaccine is given only 1 week after an MMR vaccine, the varicella vaccine should be repeated or serologic testing should be used to confirm seroconversion.
    - Live vaccines can be given in any temporal relation to "allergy shots" (ie, the same day, days before, or days after) without concern for efficacy.
- Combination vaccines
  - Are preferred by ACIP, the AAFP, and the AAP when available.
  - Are preferred by providers, parents, and, no doubt, children.
  - Reduce the number of injections required to achieve immunity.
  - The number of diseases immunized against in one injection does not "overload" the immune system; the number of antigens in the vaccines are fewer than that in a common cold.
- All vaccines for which the child is eligible should be offered whenever possible.
  - At sick and well visits, as long as the child is only mildly ill, which most believe is as long as the child is afebrile
    - Keeps the child on schedule
    - Prevents missed opportunities
    - Eliminates an additional, unnecessary office visit

Minimal Age and Intervals Between Different Doses of a Multidose Vaccine

- Vaccine doses that are given too early in life or too soon after a previous dose may be less effective. (A table of the earliest acceptable ages for administration of the routinely recommended childhood vaccines and the minimal spacing between their doses can be found at https://www.cdc.gov/vaccines/pubs/pinkbook/downloads/appendices/a/age-interval-table.pdf.)
- Does a vaccine dose given at an interval shorter than the minimal interval count?
  - State requirements for school entry vary, but ACIP considers a vaccination valid if the vaccine dose was given within 4 days of the minimal interval.
- Vaccine doses are considered invalid if an incorrectly small amount was used.
- There is a risk for side effects if an incorrectly large amount was used.
  - Steps should be taken to prevent these errors.
  - The clinician should remember that vaccination is a safe procedure, even if the child is given more than the recommended number of doses.
- Over-vaccination (vaccination with more doses than recommended).
  - With live vaccines, over-vaccination does not have adverse biological consequences because the extra vaccine virus will not infect an already immune person.
  - With inactivated vaccines, an increase in local reactions may occur if antibody levels are high.
- Prolonged intervals between doses of a multidose vaccination series do not diminish vaccine effectiveness, although the benefit of vaccination may be delayed by prolonged intervals.
- A series never needs to be restarted because of prolonged intervals (with the exception of oral typhoid vaccine).
- Late-start or interrupted schedule.
  - Some children start routine vaccination late.
  - The recommended schedule for such children is derived from the minimal intervals for the routine vaccinations.
  - A catch-up schedule is published annually with the routine schedule.
  - For a new patient whose vaccination status is unknown
    - If available, obtain a copy of the record or a report from the previous health care professional.

- If records are unavailable, the child should be presumed to be unvaccinated, and the vaccination series should be given using the accelerated schedule.
- Serologic testing can be considered for some antigens (eg, MMR, hepatitis B).

Intervals Between Vaccines and Antibody-Containing Blood Products

- Live injected vaccines (eg, MMR and varicella vaccines)
  - Must replicate in the body to induce immunity.
  - May be compromised by circulating antibodies.
- Live vaccines not administered by injection are thought to be unaffected by circulating antibodies.
  - Oral typhoid
  - OPV
- Generally, inactivated vaccines
  - Are not affected significantly by circulating antibodies.
  - Relative timing of the administration of immune globulin–containing products need not be considered.
- MMR and varicella vaccine doses given >14 days before administration of immune globulin–containing products have time to replicate and are effective.
- When live injected vaccines are given after antibody-containing blood products, the situation is more complex.
  - The specific immune globulin–containing product and its dose dictate the waiting period necessary before a live injected vaccine is given.
  - MMR and varicella vaccination should be delayed from 3–11 months, depending on the specific immune globulin preparation administered.
  - Waiting period details can be found in the AAP *Red Book* and on the CDC Web site (www.cdc.gov/vaccines/pubs/pinkbook/downloads/appendices/A/mmr_ig.pdf).

Vaccinations Administered Outside the United States

- Determining the immunization status of children who have been partially or completely vaccinated in another country can be difficult.
  - Immunization status must be determined for all children.
  - Attention must be paid to the rest of the family in the case of recent immigration.
- Vaccines, their abbreviations, and vaccination age criteria often differ among countries.
  - The first assumption to make is that the vaccines administered in other countries were as potent as those available in the United States.
  - Then, it is necessary to determine which vaccines were administered and in what doses.
    - Determining which vaccines were administered can be difficult because the standard abbreviations recorded in handheld vaccination records may be different from those used in the United States.
    - Translation of foreign-language terms can be facilitated with materials from the CDC.
  - Assistance with specific questions can be obtained from
    - Your state immunization program
    - The CDC National Center for Immunization and Respiratory Diseases
      - Telephone: 800/232-4636
      - Web site: https://www.cdc.gov/ncird/contact.html
  - Once the vaccine types are determined, schedules from the CDC can be used to determine
    - Which doses are valid
    - Which, if any, need to be repeated
  - As with vaccines administered in the United States, the CDC recommends that vaccine doses given ≤4 days before the minimum interval be counted as valid (except rabies vaccine), unless state or local requirements specify otherwise.

Contraindications and Precautions

- CDC Vaccine Contraindications and Precautions Recommendations and Guidelines (https://www.cdc.gov/vaccines/hcp/admin/contraindications.html)
- *Summary of Recommendations for Child/Teen Immunization* (www.immunize.org/catg.d/p2010.pdf)
- Anaphylactic-type allergy to a vaccine or a vaccine component
  - Includes even mild urticarial reactions
  - Contraindication to further vaccination with the vaccine in question unless the individual has been desensitized
- Encephalopathy within 7 days after a previous dose of a pertussis-containing vaccine (eg, DTaP; tetanus-diphtheria-acellular pertussis [Tdap]) not attributable to another identifiable cause
  - Contraindication to further vaccination with pertussis-containing vaccines (eg, DTaP, Tdap).

- Minor, acute illness
  - Some children are ill at the time of a well-child visit or are in need of a vaccination at an illness visit.
  - In these situations, the clinician must decide whether to recommend vaccination on the basis of 2 questions.
    - Will vaccination be safe for this ill child?
    - If the child is not vaccinated at this visit, will he or she be brought back for vaccination?
      - Past appointment-keeping behavior may help in judgment.
      - Vaccinating the ill child is best, especially if he or she has missed previous health supervision visits.
      - Persons with moderate or severe acute illness should be vaccinated as soon as the acute illness has improved.
  - Minor illnesses are not valid contraindications to vaccination.
    - Upper respiratory tract infections
    - Otitis media
    - Diarrheal illnesses, whether the individual is febrile or not
  - A second, more difficult, consideration is whether minor vaccine side effects, such as fever, will cause diagnostic confusion during the follow-up period for the illness.
    - Particularly likely to be a problem when the patient is a very young infant or newborn

Immunocompromised Children

- There are many possibilities regarding vaccinations for persons with immunocompromising conditions.
- Such persons
  - Might be at increased risk for an adverse reaction after administration of live, attenuated vaccines because of uninhibited replication, so vaccines may need to be deferred until immune function has improved.
  - May need to be revaccinated with inactivated vaccines after immune function has improved if vaccination during the period of altered immunocompetence was less effective.
  - May need certain vaccines (eg, inactivated influenza and pneumococcal vaccines) because of specific disease vulnerabilities.
- Because of the variety of immunocompromising conditions and their degree of severity, as well as the variety of vaccine-preventable diseases, vaccination of immunocompromised children often is best managed in consultation with a pediatric infectious disease specialist.
- Live vaccines.
  - In general, live vaccines cannot be used in immunocompromised individuals.
    - Potential for severe or fatal reactions from uncontrolled replication of the vaccine virus
  - Live vaccines should not be given in cases of
    - Congenital immunodeficiency
    - Leukemia
    - Lymphoma
    - Generalized cancer
    - Treatments that cause immunosuppression (eg, alkylating agents, antimetabolites, radiation therapy)
    - Persons receiving daily, large doses of corticosteroids (the equivalent of 2 mg/kg of prednisone per day) for ≥14 days
      - Live vaccines should be deferred for at least 30 days after cessation of therapy or reduction in dose.
      - Live vaccine use is not contraindicated if
        - The corticosteroid is aerosolized (as in asthma inhalers) or a topical agent.
        - It is given on an alternate-day, short course (<14 days).
        - The child is on a physiologic replacement schedule.
  - Vaccination may be considered for the following immunocompromising conditions or immunocompromised patients:
    - HIV infection
      - Limited data among HIV-infected children (CDC class N, A, or B with age-specific $CD4^+$ T-lymphocyte percentages of ≥15%) indicate that varicella vaccine is immunogenic, effective, and safe.
      - When indicated, MMR vaccination is recommended for all asymptomatic and mildly symptomatic HIV-infected persons who do not have evidence of severe immunosuppression.
      - MMR with varicella (MMRV) vaccine should not be administered to persons with HIV infection.
    - Immunocompromised people with limited humoral immunodeficiency (eg, hypogammaglobulinemia, immunoglobulin A deficiency) may be routinely vaccinated with varicella vaccine.
    - Children with deficiencies in complement or with asplenia can receive live, attenuated viral and bacterial vaccines.

  - Children with defects in phagocyte function (eg, chronic granulomatous disease, myeloperoxidase deficiency) can receive live, attenuated viral, but not bacterial, vaccines.
  - Being immunocompromised is a precaution but not a contraindication to the live, oral pentavalent rotavirus vaccine.
- Inactivated vaccines.
  - Persons with altered immunocompetence generally are advised to receive injectable influenza vaccine and age-appropriate polysaccharide-based vaccines (PCV13, pneumococcal polysaccharide, meningococcal conjugate, meningococcal polysaccharide, and Hib) on the basis of demonstrated effectiveness or an increased risk for disease if the vaccine is withheld.
  - During chemotherapy or radiation therapy
    - Vaccination should be avoided if possible (except with IIV).
    - Antibody responses might be suboptimal.
  - Patients vaccinated within 14 days before starting immunosuppressive therapy or while receiving immunosuppressive therapy should be considered unimmunized and should be revaccinated at least 3 months after therapy is discontinued if immune competence has been restored.
- Bone marrow transplant.
  - For vaccination of bone marrow transplant patients, the physician should consult the AAP *Red Book* or the *General Recommendations*.
- Household contacts
  - Should be vaccinated as indicated.
  - Should receive annual influenza vaccination (injectable).
  - MMR and varicella vaccines, which are live vaccines contraindicated for use in most immunocompromised people themselves, should be given to susceptible contacts of immunocompromised people.
  - If the varicella vaccine recipient has a rash after vaccination, direct contact with susceptible household contacts should be avoided until the rash resolves.
  - OPV, which is used outside the United States, should not be given to people who are immunocompromised or to their close contacts.
  - All members of the household should wash their hands after changing the diaper of an infant, in particular, to minimize rotavirus transmission.

Pregnancy

- Live vaccines
  - Known pregnant women generally should not receive live, attenuated virus vaccines (eg, MMR, varicella) or live bacterial vaccines.
  - Potential risks of vaccinating pregnant women are usually outweighed by the benefits when
    - Likelihood of disease exposure is high.
    - Infection would pose a risk to the mother or fetus.
    - Vaccine is unlikely to cause harm.
  - Routine pregnancy testing of women of childbearing age before administering a live-virus vaccine is not recommended.
  - Women should avoid pregnancy for 4 weeks after receiving the MMR, MMRV, or varicella vaccine.
  - If a pregnant woman is inadvertently vaccinated or becomes pregnant within 4 weeks after receiving these vaccines, she should be counseled about the theoretical basis of concern for the fetus.
  - MMR or varicella vaccination during pregnancy should not be considered a reason to terminate the pregnancy.
- Inactivated vaccines
  - Pregnant women generally may receive inactivated vaccines and toxoids.
  - Routine influenza vaccination is recommended for all women who are or will be in any trimester of pregnancy during influenza season—usually early October through late March in the United States.
  - Tdap should be given to pregnant females during each pregnancy, preferably between 27 and 36 weeks' gestation, regardless of prior vaccination with tetanus-diphtheria or Tdap vaccine.
  - The CDC recommends that hepatitis B vaccine should be given to a pregnant woman for whom it is indicated.
  - Vaccines against hepatitis A and meningococcal disease should be considered for women at increased risk for those infections.
  - IPV can be administered to pregnant women at risk for exposure to wild-type poliovirus infection.
  - HPV vaccines are not recommended for use in pregnant women, but no intervention is needed if it occurs.

Preterm Birth

- Preterm neonates should be vaccinated using the routine schedule on the basis of their chronological age (ie, time since birth, regardless of gestational age or birth weight) and the standard doses of vaccine, with 2 exceptions.
- Hepatitis B vaccine.
  - Preterm neonates born to mothers who are hepatitis B surface antigen (HBsAg) positive or with unknown HBsAg status must receive hepatitis B vaccine within 12 hours after birth.
  - This birth dose should not be included in the primary hepatitis B series; 3 more hepatitis B vaccines should be given starting at 1 month of age.
  - Preterm neonates <36 weeks of age and weighing <2,000 g at birth have shown a decreased response to hepatitis B vaccine administered before age 1 month.
  - By 1 month of age, medically stable preterm infants have shown a response to vaccination comparable to full-term infants.
  - The neonate also must be given hepatitis B immunoglobulin within 12 hours of birth unless postnatal serology shows the mother to be HBsAg negative.
- Rotavirus vaccine.
  - Deferral of rotavirus vaccine is recommended until discharge because of the concern for shedding.
  - The rotavirus vaccine series should not be initiated for infants ≥15 weeks.

Vaccine Safety

- Vaccine safety concerns have been based on
  - Data (eg, RotaShield and intussusception)
  - Speculation (eg, MMR vaccine and autism spectrum disorder)
- New concerns are likely to arise.
  - Reliable, regularly updated sources of vaccine safety information include
    - AAP
    - CDC
    - Immunization Action Coalition
    - Vaccine Education Center
    - Institute for Vaccine Safety

Inattention and Impulsivity

DEFINITION

- Inattention and impulsivity
  - Can limit adaptability to normal peer and family situations and interfere with learning
  - Are typical characteristics of preschool children
    - In many, symptoms do not rise to the level of a disorder.
    - Symptoms occurring more persistently and to a greater degree than in a child's peers may be cause for concern.

HISTORY

- Child's teacher is often the first to observe symptoms or to encourage medical attention.
- Indications in history from youth or parent include
  - Excitability, impatience, angry outbursts
  - Wandering attention
  - Difficulties with behavior
  - Academic difficulties
  - Parents and teachers presuming or seeking diagnosis of attention-deficit/hyperactivity disorder (ADHD)
- Many children do not spontaneously disclose their symptoms.
- Because observers often disagree about behavioral and emotional symptoms, collecting information from multiple sources (eg, parent, youth, teacher) can be helpful.
- The process of reconciling differences can itself be therapeutic.

PHYSICAL EXAMINATION

- Standardized wide-range psychosocial screening instruments can identify children with emotional and behavioral difficulties that include symptoms of inattention and impulsivity.
- Diagnostic criteria for ADHD require symptoms in more than one setting, so collateral reports from school and parents are critical.
- Several instruments have versions to collect information from the youth, parents, and teachers (**Table 1**).
- Use additional instruments (eg, Vanderbilt ADHD Rating Scales) to
  - Confirm findings of initial screening.
  - Corroborate a concern raised by a teacher or parent.
  - Serve as a benchmark to track treatment progress.
- Use functional assessment tool to determine whether the child is significantly impaired.
  - Impact Supplement of the Strengths and Difficulties Questionnaire (SDQ)
  - Columbia Impairment Scale
- Use tools to assess the effect of the child's problem on other members of the family (eg, Caregiver Strain Questionnaire).

DIFFERENTIAL DIAGNOSIS

- Differentiate symptoms from normal behavior; all children may be inattentive or impulsive at times.
- Further evaluate extremes; of concern is behavior that is
  - Harming family or peer relationships
  - Interfering with learning
  - Putting the child at risk for expulsion from child care or school
- Children with limited social experiences and those whose environment is relatively less structured may seem impulsive and inattentive compared with peers, especially when entering structured situations (classroom or organized group activities).
- Conditions that may mimic or co-occur with inattention and impulsivity include
  - Hearing or vision problems
    - All children who seem inattentive should be screened for sensory deficits.
  - Sleep deprivation
    - Sleep problems can cause inattention and irritability.
    - ADHD contributes to difficulty sleeping.
  - ADHD
    - Diagnosis requires a persistent pattern of inattention and/or hyperactivity-impulsivity that interferes with functioning or development.
    - Characterized as ≥6 symptoms of inattention or hyperactivity for >6 months.
    - Inattention symptoms include
      - Careless with detail
      - Fails to sustain attention
      - Seems not to listen
      - Does not finish instructed tasks
      - Poor self-organization
      - Avoids tasks requiring sustained mental effort
      - Loses things
      - Easily distracted
      - Seems forgetful

Table 1. General Psychosocial Screening/Results Suggesting Inattention and Impulsivity

Screening Instrument	Score
Pediatric Symptom Checklist (PSC)-35	• Total score ≥24 for children ≤5 years • ≥28 for those 6–16 years • ≥30 for those ≥17 years AND • Further discussion of items related to attention and impulse control confirms a concern in that area.
PSC-17	• Attention subscale is ≥7. AND • Further discussion of items related to attention and impulse control confirms a concern in that area.
Strengths and Difficulties Questionnaire (SDQ)	• Total symptom score >19 • Hyperactivity scale score of 7–10 (See instructions at www.sdqinfo.com.) • Impact scale (back of form) score of 1 (medium impairment) or ≥2 (high impairment) AND • Further discussion of items related to attention and impulse control confirms a concern in that area.

- — Hyperactivity symptoms include
  - ■ Fidgets
  - ■ Leaves seat when should be seated
  - ■ Runs or climbs excessively and inappropriately
  - ■ Noisy in play
  - ■ Persistent motor activity unmodified by social context (seen less in teens)
  - ■ Talks excessively
  - ■ Blurts out answers before question completed
  - ■ Fails to wait turn
  - ■ Interrupts others' conversation or games
- — Further features necessary to make this diagnosis include
  - ■ Symptoms present <12 years.
  - ■ Symptoms present in at least 2 types of settings (eg, home and school).
  - ■ Symptoms cause significant distress or impaired functioning.
  - ■ Symptoms not better explained by another psychiatric disorder.

- Learning problems or disabilities
  - — If inattention and impulsivity are associated with problems of school performance, the child may have learning difficulties.
- Developmental problems
  - — Children with overall intellectual or social limitations may seem less able than peers to control impulses and to maintain attention.
- Language impairment or disorder
  - — Children with receptive or expressive language impairment may be frustrated and inattentive because of difficulty understanding or being able to express themselves.
  - — Similar problems can arise when children are learning a new language and cannot yet fully function at the level of peers or teachers.
- Depression
  - — May co-occur with ADHD
  - — Depression associated with attention difficulties indicated by
    - ■ Marked sleep disturbance
    - ■ Disturbed appetite
    - ■ Low mood
    - ■ Tearfulness

- Exposure to adverse childhood experiences
  - Children who have experienced the following are at high risk for symptoms of inattention and impulsivity:
    - Trauma
    - Violence
    - Natural disaster
    - Separation from a parent
    - Parental divorce or separation
    - Parental substance use
    - Neglect
    - Physical, emotional, or sexual abuse
  - These symptoms may mask or be expressions of emotional difficulties, such as adjustment disorder or posttraumatic stress disorder (PTSD).
  - Symptoms of PTSD may resemble those of ADHD (eg, hypervigilance may mimic hyperactivity, dissociation may mimic inattention).
  - These children may also manifest other forms of anxiety.
  - Inquiring about previous trauma in a confidential setting is important.
- Anxiety
  - Anxious children may experience difficulty concentrating.
- Bereavement
  - Most children will experience death of a family member or friend in their childhood.
  - Other traumatic losses may trigger grief responses.
    - Separation or divorce of parents
    - Relocation
    - Change of school
    - Deployment of a parent in military service
    - Breakup with a girlfriend or boyfriend
    - Remarriage of parent
  - These events may result in the following behaviors immediately after the loss or more persistently:
    - Sadness
    - Anxiety
    - Difficulty concentrating
    - Poor impulse control
    - Academic decline
- Physical illness that can mimic or provoke symptoms of inattention and impulsivity
  - Thyroid disease
  - Hypoglycemia
  - Hyperglycemia
  - Side effects of medications (eg, bronchodilators)
  - Endocrine tumors (eg, rarely, pheochromocytoma)
- Substance use
  - Children with symptoms of inattention and impulsivity may self-medicate with alcohol, nicotine, or other drugs.
  - Children using substances may manifest inattention, impulsivity, and deteriorating school performance.
- Conduct or oppositional disorders
  - These disorders need to be differentiated from problems of inattention and impulsivity and ADHD.
- Tourette syndrome
  - Identify children with repetitive movements (tics).
  - In children with Tourette syndrome, ADHD symptoms may precede onset of tics.
  - Stimulant medication may worsen tics.
  - Tailor treatment to the child's most pressing symptoms before deciding the risks and benefits of using stimulants in children with both problems.

TREATMENT APPROACH

- Care can begin in the primary care setting from the time symptoms are recognized.
- Care can begin even if the child's symptoms do not rise to the level of a disorder or referral to a mental health specialist is ultimately part of the care plan.

SPECIFIC TREATMENT

- Engage child and family in care.
  - Without engagement, most families will not seek or persist in care.
  - The process may require multiple primary care visits.
  - Reinforce strengths of the child and family as a method of engagement.
    - Good relationships with at least one parent or important adult
    - Prosocial peers
    - Concerned or caring family
    - Help seeking
    - Connection to positive organizations
  - Identify barriers to addressing the problem.
    - Stigma
    - Family conflict
    - Resistance to treatment
  - Use "common factors" techniques to build a therapeutic alliance with the child and family (**Box 1**).

Box 1. HELP Build a Therapeutic Alliance

H = Hope

Increase the family's hopefulness by describing your realistic expectations for improvement and reinforcing the strengths and assets you see in the child and family.

E = Empathy

Communicate empathy by listening attentively.

L^2 = Language, Loyalty

Use the child's or family's own language to reflect your understanding of the problem as they see it and to give the child and family an opportunity to correct any misperceptions.

Communicate loyalty to the family by expressing your support and your commitment to help.

P^3 = Permission, Partnership, Plan

Ask the family's permission for you to ask more in-depth questions or make suggestions for further evaluation or management.

Partner with the child and family to identify any barriers or resistance to addressing the problem, find strategies to bypass or overcome barriers, and find agreement on achievable steps aligned with the family's motivation.

Establish a plan (or incremental first step) through which the child and family will take some action(s), work toward greater readiness to take action, or monitor the problem, and then follow up with you, based on the child's and family's preferences and sense of urgency. (The plan might include, for example, gathering information from other sources such as the child's school, making lifestyle changes, applying parenting strategies or self-management techniques, reviewing educational resources about the problem or condition, initiating specific treatment, seeking referral for further assessment or treatment, or returning for further family discussion.)

From American Academy of Pediatrics. *Addressing Mental Health Concerns in Primary Care: A Clinician's Toolkit* [CD-ROM]. Elk Grove Village, IL: American Academy of Pediatrics; 2010.

- Reach agreement that there is a reason to consider intervention and that there are concrete problems that the family would like to address.
- Regardless of other roles, the primary care physician can encourage a positive view of treatment.

■ Offer psychoeducation about ADHD, the differential diagnosis, and the process of arriving at a diagnosis.
- Parents have likely heard about ADHD from other sources.
- Knowledge and concerns about the conditions may vary widely.
- Parents may have worries about being coerced into labeling their child with the condition by demands from the pediatrician or schools.
- Clinician can
  - — Ask what they know and what questions they may have.
  - — Explain the process of making a provisional diagnosis and investigating alternatives.
    - ■ Language and learning problems
    - ■ Anxiety
    - ■ Normal variation in development and temperament
  - — Assure parents that physician will work with them to
    - ■ Collect relevant information.
    - ■ Make a plan of treatment.
    - ■ Reevaluate the situation as time goes on.
- Parents will want to know more about the natural history of the condition and implications for their child's future.
- Reasonable to say that these problems are
  - — Common
  - — Amenable to treatment
  - — Usually more easily managed as the child gets older

- Encourage healthy habits.
  - Regular exercise and outdoor play.
  - These children may also benefit from participation in structured sports, which offer exercise and the opportunity to build social skills.
    - Taking turns
    - Following rules
    - Handling success and disappointment
  - Also important are
    - Regular sleep habits
    - Special time with parents
    - Praise for good behavior
    - Reinforcement of the child's strengths
    - Limiting media exposure
      - Television programs, movies, and computer games can be overstimulating.
      - Long hours in these activities can produce irritability.
      - Unrestricted access to a television or computer, especially in the child's bedroom, can contribute to
        - Loss of sleep
        - Failure to do homework
        - Risk of seeing programming that contributes to increased activity
- Reduce stress.
  - Consider the child's social environment.
    - Family social history
    - Parental depression screening
    - Results of any family assessment tools
    - Reports from child care or school
  - Symptoms of inattention and hyperactivity will generally worsen in stressful settings.
  - Role of physician.
    - Guide parents in providing a safe, structured environment.
    - Coach parents in working constructively with the school.
    - Address stresses on family members.
- Offer initial intervention(s).
  - Guide parents in managing the child's behavior.
    - Tangible rewards or privileges
      - Contingent on performance of routine tasks (eg, TV or computer time for attaining a realistic goal)
      - Most effective when coupled with a system for helping the child be aware of level of functioning, including charts that monitor
        - Events such as completion of homework without a reminder
        - Staying "on task" in school for a prearranged time before taking a break
        - Carrying out chores at home before being asked
    - Parent praise
      - Conscious effort to identify and comment on positive behavior (eg, compliment child, especially when action is spontaneous).
    - Parent monitoring
      - Systematic means to rate the child's burden of specific ADHD symptoms and social, emotional, and academic function (eg, weekly use of Vanderbilt scales or a customized checklist, often with simultaneous teacher ratings).
      - Helps the parent advocate for the child; offer short-term, objective measures of progress.
    - Time-out
      - Avoiding reinforcement of undesired behavior through arguing or allowing the behavior to continue (eg, child is required to sit without attention or activity for a brief period as a consequence for undesired behavior)
    - Commands/limit setting
      - Use clear, simple commands that give the child
        - Warning of impending expected behavior
        - Opportunity to perform it
        - Warning of consequences for nonperformance
        - Consistent consequence (eg, "You can do one more puzzle and then we have to go…now it's time to go…if you don't put the puzzle away now, you can't chose the music we listen to in the car.")
  - If there are battles over homework, offer guidelines (**Box 2**).
- If child meets diagnostic criteria for ADHD, consider specific therapy.[1]
  - Treatment depends on age and should be noted in the overall care plan.
  - Preschool-aged children (4–5 years of age).
    - Evidence-based, parent- or teacher-administered behavior therapy is first line of treatment (quality of evidence A/strong recommendation).

Box 2. Suggestions for Parents to Consider in Addressing Homework Issues

- Obtain consent for the clinician to exchange information with the child's teacher.
- Establish constructive 3-way (parent, teacher, pediatrician) communication with the school.
- Ask if testing has been requested and taken place to detect special educational needs.
- Monitor academic progress, helping to reinforce successes and identify particular subjects or educational settings where more support is needed.
- Advocate for appropriate classroom strategies.
- Have the child sit at the front of the class.
- If possible, engage the child in active learning (eg, have the child go to the board to write answers to questions).
- Give extra time to stay organized (eg, write down assignments, make sure that all needed materials are taken home or gathered for a project, have the child repeat back what he or she is to do).
- Break longer assignments into shorter pieces (also helpful for homework).
- Coordinate reports of behavior with home—consider a daily report card of behavior and subsequent rewards or consequences.

  - May prescribe methylphenidate if the behavior interventions do not provide significant improvement and there is moderate to severe continuing disturbance in the child's function.
  - In areas in which evidence-based behavioral treatments are not available, the clinician needs to weigh the risks of starting medication at an early age against the harm of delaying diagnosis and treatment (quality of evidence B/recommendation).
- Elementary school-aged children (6–11 years of age).
  - US Food and Drug Administration-approved medications for ADHD (quality of evidence A/strong recommendation) and/or evidence-based parent- and/or teacher-administered behavior therapy (preferably both) (quality of evidence B/strong recommendation).
  - Evidence is strong for stimulant medications and sufficient but less strong for atomoxetine, extended-release guanfacine, and extended-release clonidine (in that order) (quality of evidence A/strong recommendation).
  - The school environment, program, or placement is a part of any treatment plan.
- Adolescents (12–18 years of age).
  - US Food and Drug Administration-approved medications for ADHD with the assent of the adolescent (quality of evidence A/strong recommendation) and may prescribe behavior therapy as treatment for ADHD (quality of evidence C/recommendation), preferably both
  - Primary care clinicians should titrate doses of medication for ADHD to achieve maximum benefit with minimum adverse effects (quality of evidence B/strong recommendation).

■ Provide resources.
- Families may find support and resources from organizations such as Children and Adults With Attention-Deficit/Hyperactivity Disorder (www.chadd.org).
- Provide contact numbers and resources in case of emergency.

WHEN TO REFER

■ Involve specialist(s) if the child does not respond to initial interventions or if the following clinical circumstances exist:
- Child has severe functional impairment.
- Child has severely disruptive behavior or aggression.
- Child has comorbid depression or PTSD.
- Child's problems with mood, behavior, and development seem more prominent than difficulties with attention or impulsivity.
- Symptoms are threatening school performance or achievement of other developmentally important goals (eg, developing and sustaining friendships).
- The child or parent is very distressed by the symptom(s).

- There are co-occurring behavior problems.
  - The combination of shyness, anxiety, and behavior problems is thought to be particularly risky for future behavior problems of a more serious nature.
- The child's symptoms were preceded by serious trauma.
- The child has ADHD and contraindications to stimulants or marked side effects with stimulants.
- The child's problems occur in the context of other family emotional or behavioral problems that have not been alleviated with primary care interventions.

- When specialty care is needed, ensure that it is evidence informed and assist the family in accessing it.
- Pharmacologic interventions and many evidence-based and evidence-informed psychosocial interventions are available for the treatment of ADHD.
- Ideally, those referred for care in the mental health specialty system would have access to the safest and most effective treatments.
- Youth referred for mental health specialty care complete the referral process only 61% of the time.
- A significantly smaller number persist in care.
- Not all evidence-based interventions may be available in every community.
- If a particular intervention is not available, collaborate with others in the community to advocate on behalf of children.
- Increasingly, states offer telepsychiatry services and consultation/referral support "warmlines" that help physicians provide initial treatment and locate resources.
- The availability of the latter form of help is tracked at the National Network of Child Psychiatry Access Programs (www.nncpap.org).
- Reach agreement on respective roles in the child's care.
- If the child is referred to mental health specialty care, the physician may be responsible for
  - Initiating medication or adjusting doses
  - Monitoring response to treatment
  - Monitoring adverse effects
  - Engaging and encouraging the child's and family's positive view of treatment
  - Coordinating care provided by parents, school, medical home, and specialists
- The child may improve just knowing that the clinician is involved and interested.

FOLLOW-UP

- Monitor progress toward therapeutic goals.
  - Child care reports
  - Preschool and school reports
- Monitor symptoms and functioning.
  - Vanderbilt scales (parent and teacher)
  - SDQ (parent, teacher)
  - Pediatric Symptom Checklist
- Carefully titrate medications and behavioral treatments to achieve desired effects without side effects.
- The need for higher-than-recommended doses of medication could indicate difficulties with adherence or a need to change medications.
- Behavioral treatments can be difficult to implement and maintain.
- Help adapt behavioral suggestions to family circumstances and explore barriers to other aspects of treatment, including effective engagement with schools.
- Help the family understand it is not uncommon for treatment to be successful and then seem to lose effectiveness.
  - With new stresses or demands or when there has been a letup on treatment after a period of success
- Consider new treatments or diagnoses if modifying existing treatment and exploring ways of dealing with new stresses do not help get function back to baseline.

REFERENCE

1. Adapted from American Academy of Pediatrics. *ADHD: Caring for Children With ADHD: A Resource Toolkit for Clinicians* [CD-ROM]. 2nd ed. Elk Grove Village, IL: American Academy of Pediatrics; 2011

DEFINITION

- Inflammatory bowel disease (IBD) is a group of chronic, relapsing inflammatory conditions affecting the digestive system.
- IBD is characterized by inflammation generally limited to
  - Colonic mucosa in patients with ulcerative colitis (UC)
  - Discontinuous transmural intestinal inflammation in patients with Crohn disease (CD)

SIGNS AND SYMPTOMS

- Presenting symptoms include
  - Diarrhea
  - Hematochezia
  - Abdominal pain
  - Fever
  - Weight loss
  - Growth delay
- Diarrhea is present in 70%–85% of patients diagnosed with IBD.
- However, a patient's predominant complaint may be less obvious and may change depending on patient age or location of disease.
  - UC and CD: Diarrhea and abdominal pain are common.
  - CD: ≤35% of patients have altered growth and development.
  - UC: Growth problems may occur only 10% of the time.
- Bloody diarrhea occurs in most patients with UC (90%), while CD patients experience this 15%–60% of the time.
- Pain or cramping is common.
  - Location of pain (particularly right lower-quadrant pain) may be confused with appendicitis pain.
- Stooling history should be elicited and could be described as tenesmus, urgency, anal pain, labial pain, or other symptoms surrounding defecation.
- Patients may present with intestinal complications that differ by diagnosis.
  - UC: Toxic megacolon may develop.
    - Colon becomes large and dilated.
    - Associated with hemodynamic instability, extreme pain, and decreased bowel sounds and may lead to bowel perforation.
  - CD: Vomiting, fever, abdominal fullness, pain related to obstruction, intra-abdominal abscess, or fistulae, especially perianal.
- Extraintestinal symptoms are present in more than half of patients, often at diagnosis, and may include
  - Arthralgias or arthritis.
  - Liver disease (autoimmune hepatitis or primary sclerosing cholangitis).
  - Skin manifestations (erythema nodosum or pyoderma gangrenosum).
  - Ocular findings (uveitis or iritis).
  - Aphthous ulcers in the mouth are common in CD.
    - Other lesions may occur in the mouth or tongue and may point to deficiencies in micronutrients such as zinc or iron.
- Patients with CD may be more affected by growth and puberty delay than patients with UC.
- CD or UC may put patients at risk for slow weight gain, growth failure, or altered bone health related to nutrition, chronic inflammation, and steroid exposure.

DIFFERENTIAL DIAGNOSIS

- Diarrhea.
  - Among the most common presenting complaints
  - Unreliable on its own to diagnose IBD
- Initial differential diagnosis should include infectious causes of diarrhea because they are common in the general population.
  - Bacteria including *Clostridium difficile*
  - Viruses
  - Parasites such as *Giardia* or *Cryptosporidium*
- In the setting of weight loss or other concerning symptoms, consider
  - Malabsorptive conditions (eg, celiac disease, pancreatic insufficiency)
  - Immune deficiency
  - Bacterial overgrowth (particularly in the setting of previous bowel surgery)
  - Hormonal causes (rare endocrine tumors such as VIPomas, hyperthyroidism)
- In the absence of weight loss or other red flags, irritable bowel syndrome may be a potential etiology for non-bloody diarrhea.
- Bloody diarrhea.
  - Should be investigated with infectious testing
  - Other causes
    - Vascular abnormalities
    - Cancer or polyps (rare in childhood)
    - Other inflammatory conditions, such as Behçet syndrome
    - Toxin-mediated conditions, such as nonsteroidal anti-inflammatory drug exposure

- Endoscopic and histologic criteria to differentiate between CD and UC (or indeterminate colitis if a diagnosis is not yet available) to
  - Guide therapeutic or surgical options.
  - Determine prognosis.
- At time of diagnosis, differentiation can sometimes be made by examining distribution and location of disease.
  - UC typically has continuous involvement of part or the entire colon.
  - CD may be patchy and can affect any part of the luminal gastrointestinal (GI) tract.
- These features may not be straightforward.
  - UC may be associated with mild gastritis and "backwash ileitis" from adjacent inflammation of the colon.
  - CD may affect the colon only.
- More commonly associated with CD.
  - Microscopic criteria (eg, patchy disease, granulomas, transmural disease)
  - Segmental nature, sometimes with deep linear ulcers at diagnosis, segmental colitis, or findings of perianal disease
  - Complications such as stricture disease or internal abscesses

DIAGNOSTIC APPROACH

- Determine which patients may be evaluated as outpatients and which need to be admitted for diagnostic testing.
- Vital signs to evaluate for volume depletion related to fluid or blood loss (symptoms may have been present for months prior to diagnosis).
- History to determine
  - Timing of diarrhea (>2 weeks may be more likely to be associated with IBD)
  - Presence of blood
  - Waking at night to defecate (may differentiate more benign forms of diarrhea such as irritable bowel syndrome)
- Examine for signs of chronic disease (eg, pallor, wasting, growth problems).
- Abdominal examination to
  - Evaluate location and nature of pain.
  - Assess for possible complications.
    - Obstruction (distention, decreased bowel sounds)
    - Perforation (abdominal rigidity, pain, decreased bowel sounds)
    - Areas of fullness or mass suggestive of abscess
- Rectal examination (inspection and digital examination).
  - Patients with CD will often have anal tags, fissures, or fistulae.
  - Easily missed on symptom elucidation.
- Signs of extraintestinal manifestations (eg, oral lesions, erythema nodosum, liver involvement).
- Test for occult blood.

LABORATORY FINDINGS

- There is no single laboratory marker diagnostic for IBD.
- Common tests include
  - Inflammatory markers (erythrocyte sedimentation rate [ESR] and C-reactive protein).
  - Elevated acute phase reactants (eg, elevated white blood cell count and platelet count).
  - Hemoglobin for patients with chronic symptoms or bloody diarrhea, as these patients are likely to be anemic.
  - Albumin is a marker of malabsorption or protein losses.
- Almost 30% of patients with mild IBD may have normal ESR, hemoglobin, platelet count, and albumin.
- Stool biomarker of inflammation, such as fecal calprotectin, may identify at-risk individuals.
  - Neutrophil protein elevated in many types of intestinal inflammation, including infection
  - ≤92% sensitivity and 76% specificity as a screening tool for IBD
  - Correlates with mucosal inflammation
  - May predict relapse
  - May be used to monitor response to medical therapies
- Genetic predictors and biomarkers for IBD may help predict disease activity over time.
  - >100 genes have been identified as potential contributors to IBD.
    - *NOD2* is among the most extensively studied as risk for more aggressive course of CD.
  - Biomarkers.
    - Typically antibodies to microbes in the GI tract.
      - Antineutrophil cytoplasmic antibodies
      - Anti-*Saccharomyces cerevisiae* antibodies
      - Antibody to *Escherichia coli* outer membrane porin
    - Patterns of biomarker positivity may differ by diagnosis (UC vs CD) but may be better suited to predict risk of disease complications among patients with CD.

- Presence or absence of biomarkers is not typically useful for diagnosis of IBD (particularly as a single test).
  - May be present in the general population
  - Often absent in children with IBD

IMAGING

- Imaging is a necessary part of the early diagnostic workup of patients with IBD and often is needed after diagnosis.
- Potential reasons for imaging include
  - Categorizing disease extent
  - Evaluating for complications
  - Monitoring response to treatment
- Plain abdominal radiography.
  - Typically for acute changes or emergencies (vomiting, acute pain, distention, concern for perforation or bowel obstruction)
- Upper GI series with small-bowel follow-through (plain radiographs with ingested contrast).
  - Widely used and well tolerated for small bowel disease extent, particularly if there is no concern for an intra-abdominal process (abscess, stricture, fistula) or perianal disease.
- Magnetic resonance imaging (MRI) and computed tomography (CT).
  - Evaluation of disease extent
  - Identification of intra-abdominal abscesses and fistulae
  - Enterography with oral contrast designed to distend the bowel wall and glucagon to change GI motility
    - Provide additional information about areas of narrowing or stricture and intra-abdominal complications; may identify other extraintestinal complications.
  - MRI of the pelvis for evaluation of perianal disease that cannot be properly evaluated by an IBD surgeon or if complex perianal disease is suspected
  - Standard abdominal CT for more urgent evaluation of complications
- Ultrasound.
  - To evaluate for disease extent and intra-abdominal complications, but may be limited by operator experience and body habitus.
  - Endoscopic ultrasound and pelvic ultrasound are available but are more invasive and require special expertise for interpretation.

DIAGNOSTIC PROCEDURES

- Conventional ileocolonoscopy and microscopic examination of biopsy specimens remain the gold standard for diagnosis of IBD.
- Entire colon and ileum should be examined because visualization of the distal colon only with proctosigmoidoscopy may not give enough information to make an appropriate diagnosis.
- Endoscopic examination of the upper digestive tract
  - May help differentiate among types of disease in children.
  - Not absolutely necessary.
- Endoscopic biopsies are crucial to help classify disease.
- Endoscopy after diagnosis may be needed if a change in therapy is being considered or to examine for dysplastic changes after diagnosis.
- If the small intestine cannot be examined visually during upper or lower endoscopy, capsule endoscopy (use of a wireless ingested camera to visually examine the mucosa) may provide assessment of disease extent but cannot provide biopsies.

TREATMENT APPROACH

- Treatment of IBD depends on
  - Degree of severity
  - Disease location
  - Potential complicating features, such as fistulae or abscesses
- Goals of therapy
  - Relieve symptoms.
  - Minimize side effects of medications.
  - Ensure adequate growth.
  - Maintain good quality of life.

SPECIFIC TREATMENTS

- For mild disease presentations, first-line therapy would usually include aminosalicylates such as mesalamine.
- For disease affecting the rectosigmoid area, topical therapy, such as mesalamine suppositories or enemas.
- For more moderate disease activity, corticosteroids are normally used to induce remission.
  - Alternate therapy will be needed for maintaining remission.

- Maintenance medications include immunomodulators or enteral therapy.
  - Potential side effects of immunomodulators need to be discussed and screened for periodically.
    - — Bone marrow toxicity
    - — Hepatotoxicity
    - — Risk of malignancies
- Enteral therapy is effective in inducing and maintaining remission in ≤85% of patients with CD when treated.
- For severe disease, step-up therapy with biologicals is usual, with pediatric response rates >80%.
- Drugs from different therapeutic classes may be used additively.
- For some patients with complicated disease (eg, fistulas, growth delay, severe UC), a step-down approach with early introduction of stronger agents, such as antitumor necrosis factor (TNF) agents, may prevent progression of complications and improve outcomes.
- Surgical consultation and intervention for bowel resection may be necessary for some patients with refractory disease or bowel obstruction or perforation.

WHEN TO ADMIT

- Recurrent fevers or concerns for abscess
- Persistent vomiting or bloody diarrhea suggesting obstruction, dehydration, or need for blood transfusion
- Severe abdominal pain and distention suggesting toxic megacolon (severely dilated colon)
- Significant malnutrition for nutritional rehabilitation with oral supplementation or intravenous hyperalimentation

WHEN TO REFER

- Refer patients thought to be at risk for IBD to a gastroenterologist for appropriate diagnostic procedures and a formal diagnosis.
- Red flags that would warrant referral to a gastroenterology subspecialist include historical factors such as
  - Poor growth or weight loss
  - Persistent rectal bleeding with no obvious source on examination
  - Recurrent perirectal abscess
  - Laboratory values that may warrant referral to a GI specialist include
    - — Microcytic anemia
    - — Elevated acute phase reactants
    - — Hypoalbuminemia

FOLLOW-UP

- Approach to outpatient pediatric care of patients with IBD should be similar to that of children without chronic disease.
- Special attention should focus on growth and developmental complications, infectious risk, and malignancy risk.
- Patients with IBD may see the GI specialist only once or twice a year, so the GI specialist and primary care physician should comanage certain parts of every visit.
  - Growth and development (height and weight at every visit)
  - Assessing psychological coping
  - Complete physical examination
- Communication between the primary care physician and GI specialist is critical, with some expectations set out up front for
  - General pediatric care
  - Need for GI specialist input
  - Monitoring potential medication side effects (eg, bone marrow and hepatotoxicity with immunomodulators)
  - Growth parameters
- Perform a routine physical examination at every visit to assess for
  - Intestinal complications
  - Drug toxicity
  - Malignancy (particularly skin and lymphatic systems)
- Vaccinations.
  - General pediatrician should maintain routine vaccinations if possible.
  - Vaccination for influenza or vaccination boosters for nonresponders (eg, hepatitis B) can be given whenever the patient is medically able to receive them in an effort to avoid return visits.
- Every effort should be made to return the patient to the primary care physician for coordination of services, particularly if patients see multiple providers for other conditions.
- Gastroenterologist should remain available for GI-related issues (ie, weight loss, vomiting or diarrhea, change in abdominal pain, ongoing fever, or concern for flare).
- Clinic notes or a medical passport may be helpful in detailing ongoing issues and facilitating communication.

- Cancer surveillance.
  - Recommended to begin at ~8 years from diagnosis and then every 1–3 years.
  - Medications used for IBD may impose a slightly higher rate of skin-related cancers, so a skin examination should be performed at routine visits.
- Patients living with any chronic disease may struggle with coping and psychological issues surrounding their disease.
  - Pediatric patients with IBD experience anxiety, depression, body image issues, and social isolation.
  - Screen for these issues and offer access to psychologists early in the disease course, if possible.
  - Patients and families may benefit from support groups and services and should be encouraged to seek resources even if they feel they are coping well.
  - These resources may provide additional benefits (eg, education, self-management skills, answers to common questions or concerns).

COMPLICATIONS

- Patients requiring medications affecting the immune system (eg, steroids, TNF-α inhibitors, immunomodulators) have a higher rate of serious infections.
- GI infections, particularly *C difficile*, are a common reason for hospitalization among patients with IBD and have a high recurrence rate.
- Other risks for patients with IBD include nutritional and potential oncologic complications.
  - Suboptimal bone health related to a variety of factors (eg, frequent steroids, suboptimal nutritional status, inflammation), increased risk for osteopenia or osteoporosis, and increased fractures.
  - Vitamin deficiencies may occur in patients who have had bowel resections and should be monitored closely.
  - Patients with IBD, particularly with colitis, are at a 1.5- to 2-times higher risk of colorectal cancer, and patients with younger onset of disease may have a still higher risk of developing disease.
  - Some medications (particularly immune modulators) may be associated with an increased risk of lymphomas, but these risks remain small in proportion to the risk of untreated disease.

PROGNOSIS

- IBD does not affect overall life expectancy, but patients may have significant morbidities related to disease progression.
- Many patients with IBD, particularly patients with childhood-onset disease, may have more severe disease resulting in hospitalization or surgery.
- ≤30% of patients with CD and UC require surgery within the first 5 years after diagnosis.

PREVENTION

- Patients with IBD should receive all recommended childhood vaccinations, with some potential adjustments based on medications.
- Patients on corticosteroid therapy may not respond to vaccinations, so vaccinations should be given before starting therapy or 3 months after they have stopped therapy.
- Patients on immunosuppressive medications should not receive live-virus vaccinations; live-virus vaccines should be administered prior to the need for immunosuppressives.
- Varicella and hepatitis B should be intentionally investigated prior to initiating therapy because of risk of severe disease associated with some types of treatments, particularly anti-TNF.
  - If varicella exposure is unknown or if vaccination is uncertain, titers should be checked and vaccine administered prior to starting therapy (if appropriate for the clinical condition).
  - Latent hepatitis B may be reactivated in the setting of anti-TNF therapy, and patients with IBD may have a lower rate of immunity to hepatitis B vaccine, so hepatitis B surface antibody and antigen should be considered before initiation of these agents.

DEFINITION

- Insect bites and stings
  - Insects and arachnids (mites, ticks, and spiders) can produce anaphylaxis or act as vectors of serious or fatal disease.
    - Viral encephalitis
    - Malaria
- Infestation
  - Pediculosis (lice)
    - Capitis (scalp)
    - Palpebrarum (eyelashes)
    - Corporis (limbs and trunk)
    - Pubis (pubic area)
  - Scabies
    - Highly pruritic dermatosis caused by mites

SIGNS AND SYMPTOMS

Insect Bites

- Discrete, erythematous or flesh-colored papules, nodules, wheals, vesicles, or bullae
  - Some bites have central puncta or vesicles; others are capped by pustules or by hemorrhagic or serous crusts.
  - Usually pruritic.
  - Excoriations created by scratching are common.
- Often clustered
  - Linear or arcuate pattern, especially when caused by a crawling insect
  - Most commonly found on surfaces not covered by clothing
- Sensitized child (prior exposure)
  - Larger nodules or blisters are a robust reaction to insect- or arachnid-associated toxins.
- Unsensitized child
  - Discomfort varies from mild itch to pain caused by toxin injection.

Pediculosis

- Pediculosis capitis
  - Grayish, crawling, 6-legged louse may be seen in areas of thick terminal hair growth close to the scalp.
    - Louse eggs (nits) may be seen as minute, white-gray fixed attachments to hair shafts.
    - Nits or the insects themselves may be visible on the eyelashes or pubic hair.
  - Pruritus
    - Sometimes accompanied by erythematous papules (bites), 1–2 mm in diameter
    - Noted around the nape of the neck and the hairline, especially posteriorly
  - Other possible signs
    - Cervical adenopathy
    - Urticarial-like changes
    - Involvement of other body areas
  - Family members
    - Should be examined for head lice, especially if combs, towels, and other personal items are shared
- Pediculosis pubis
  - Often sexually transmitted.
  - Affected individuals may have other sexually transmitted infections.
- Pediculosis corporis
  - Should be suspected when widespread pruritus is present.
  - In most instances, the body louse and nits are not found on the body but in the seams of clothing or bedding.
  - Bites consist of erythematous macules and papules, which are often obscured by the results of scratching.
    - Excoriation
    - Impetiginization
    - Eczematization
    - Overt infection
    - Pigmentation

Scabies

- Highly pruritic dermatosis.
  - In the setting of worsening or persistent widespread pruritus, a diagnosis of scabies must be considered, especially if close contacts are also itching.
  - The distribution of skin changes is often the best clue to the diagnosis, along with itching that is more widespread than the objective skin findings.
- Varied and protean manifestations.
  - Ranges from rare scattered erythematous papules to widespread eczematous dermatitis and excoriations.
  - Multiple areas of mite-laden, crusting, eczematoid lesions with excoriation (Norwegian scabies).
  - As eggs hatch, repeated infestation of host leads to more rapid development of itching and other manifestations, often within 24–96 hours.

- Common sites of infestation.
  - Digital web spaces
  - Extensor surface of the elbows and knees
  - Flexor aspect of the wrists
  - Axilla
  - Upper trunk
  - Groin
- Infants.
  - Involvement of palms and soles, especially with vesicles
  - Skin changes on the face and head
- Burrows created by female mites.
  - Help establish diagnosis in some patients
  - Often disguised by excoriations, eczematous reactions, or superimposed infection
- Family members, sexual partners, and other close contacts of index cases should be examined when possible.
  - The patient's history may reveal that several people in a household are itching.
  - Fomites rarely transmit scabies, especially in temperate climates.
  - Although humans may acquire subspecies of scabies mites that infest other mammals, such infestation is self-limiting, as other mite subspecies do not reproduce in human skin.

DIFFERENTIAL DIAGNOSIS

- For scabies, the differential diagnosis includes insect bites and papular urticaria and various forms of eczematous dermatitis and folliculitis.

DIAGNOSTIC APPROACH

- Insect bites
  - Discrete, erythematous, or flesh-colored papules, nodules, or wheals, usually pruritic, suggest the diagnosis of insect or arachnid bites.
  - Excoriations or changes consistent with dermatitis (reddish, ill-defined areas with an altered surface texture and often scaling or scale crust) are common.
- Infestation
  - In pediculosis, the louse or nits will be found in thick terminal hair or on fomites.
  - Pediculosis corporis should be suspected when widespread pruritus is present along with erythematous papules and signs of scratching, especially on covered or hairy body areas.
  - Clinical diagnosis of scabies is based primarily on the distribution of erythematous papules, nodules, or other inflammatory changes and, where present, more specific findings, such as burrows.
  - Worsening or persistent widespread pruritus suggests scabies.
    - Especially if close contacts are also itching.
    - Distribution of skin changes (eg, digital web spaces) is also a clue.

LABORATORY FINDINGS

- Light microscopy
  - Diagnosis of scabies in infants
    - A drop of mineral oil is placed on the skin.
    - Scrapings of burrows or papules from palms or soles are removed by scalpel.
    - Confirmatory ova, mites, or feces are revealed under low magnification.

TREATMENT APPROACH

- Insect bites
  - Topical antipruritic products such as calamine
  - Cold packs
  - Topical corticosteroid creams
  - Oral antihistamines
- Pediculosis
  - Head lice.
    - Physical removal is as effective as drug treatment.
    - Mechanical means of removal, especially using surface agents such as silicone.
    - Chemical treatments should be avoided in infants.
    - Pediculosis palpebrarum can be treated by applying plain petrolatum to eyelashes 4–5 times daily and is required for 8–10 days.
  - Body lice.
    - Total body application of 5% permethrin cream for 8–14 hours
  - All methods depend on following instructions carefully.
  - All methods will need to be repeated.
  - Clothing, bedding, combs, towels, and other items used by lice-infested persons should be washed in hot water.
  - All clothing, stuffed animals, comforters, etc that cannot be washed or dry-cleaned should be stored in a plastic bag and sealed for 2 weeks.
- Scabies
  - Should be treated regardless of symptoms
    - 5% permethrin to the entire body, except the face

SPECIFIC TREATMENTS

Insect Bites

- Topical corticosteroid creams plus oral antihistamines.
  - Primary treatment
  - Reduces inflammation and pruritus
- Topical antipruritics (calamine) and cold soaks/ice.
  - Soothing
- Topical antihistamines should be avoided.
  - Ineffective
  - May cause allergic contact dermatitis
- Oral systemic corticosteroids (rare cases).
  - Sometimes indicated for
    - Extensive bites
    - Hypersensitivity manifesting as papular urticaria or in other ways that involve >20% of the body
  - ≤1-week course of ~0.5 mg/kg of prednisone or equivalent.
    - Longer-term or chronic treatment is not indicated for this circumstance alone.
  - Topical therapy should be started at the same time.
    - Prevents rebound phenomenon
  - All contraindications must be excluded.
    - The risk of adverse events, although small with brief treatment courses, must be considered.

Pediculosis

- Head lice, pubic lice.
  - Physical removal of lice and eggs
    - Careful, repeated removal of head lice has shown superior results to drugs, even malathion.
    - Kits are available.
  - Chemical treatment
    - Resistance to chemical agents is increasing.
    - Chemical treatments are used only with great caution by pregnant or nursing women and should be avoided by persons with allergies to any component of the treatment.
    - Infants should not be treated unless essential and only with very close supervision.
  - Pyrethrins
    - Several nonprescription preparations are available.
    - Nix cream rinse contains 1% permethrin.
    - A fine-toothed comb can be used to remove nits from hair shafts after chemical treatment.
    - Retreatment is usually necessary ~1 week after the first application to kill lice that have hatched from viable nits that were not killed initially.
  - Malathion 0.5% solution
    - Must be left on for 8–12 hours
    - Flammable
  - Dimethicone 4%
    - Recently found to be effective
  - Other insecticides
    - Lindane (gamma-benzene hexachloride [GBH]) is more toxic and probably less effective with much resistance and should only be used when all other treatment options have failed.
      - California has banned lindane for human use because of its neurotoxicity.
    - Oral ivermectin.
      - 2 doses given 7 days apart are effective for treatment of several kinds of lice infestation.
      - This application is an off-label use.
- Body lice.
  - Total body application of 5% permethrin cream (Elimite) for 8–14 hours
    - May be necessary to apply to the hair
  - A limited number of treatments spaced ~7 days apart may be required for eradication, using various pediculicides, such as
    - Permethrin
    - GBH
    - Pyrethrins
    - Vinegar rinse to remove stubborn nits
  - Pruritus
    - May continue for ≥2 weeks after treatment.
    - Patients should be advised that itching might continue, so that they do not overtreat themselves through repeated applications.
    - Oral antipruritics, soothing bland lotions, and topical corticosteroids can help.
- Pediculosis palpebrarum.
  - Apply plain petrolatum to the eyelashes 3–5 times daily.
    - Treatment is required for ~8–10 days.
  - A moustache comb can be used daily to remove lice and nits from the eyelashes.
    - Other infested body areas should be treated simultaneously.
  - If this method fails, physostigmine 0.25% may be similarly applied to eyelashes.
    - Usually curative in 3 or 4 days but may interfere with vision.

- All potentially infested items should be treated with wet or dry heat (or both).
  - Minimum of 65°C (149°F) for minimum of 15 minutes (preferably ≥30 minutes)
    - Clothing
    - Bedding
    - Combs
    - Towels
  - Clothing, stuffed animals, comforters, and other items that cannot be washed or dry-cleaned
    - Store in a sealed plastic bag for 2 weeks.

Scabies

- Should always be treated, regardless of symptoms.
  - Patients may be asymptomatic carriers.
  - Chemical treatments are used only with great caution in
    - Pregnant or nursing women
    - Infants
    - Persons with allergies to any component of the treatment (should be avoided)
- Permethrin 5%.
  - Thorough application to the entire body, except the face
  - Treatment of choice because of high efficacy and relatively low toxicity
- Alternate treatments.
  - Lindane or a similar GBH preparation
    - Probably less effective than permethrin.
    - Lindane is associated with irritant dermatitis.
    - GBH is associated with adverse reactions and toxicity.
    - Should be dispensed in limited quantities and used only when other treatment options have failed.
    - Parents should be informed about possible neurotoxicity and other complications from organophosphate exposure.
    - Repeated treatments, especially when based only on symptoms, should be actively discouraged.
  - Crotamiton 10% (Eurax)
    - Probably less efficacious
    - Must be applied at least twice
  - Benzyl benzoate
    - Widely used as an inexpensive emulsion, sometimes recommended by the World Health Organization.
    - Not available in the United States.
- If topical treatment fails or is not feasible.
  - Oral ivermectin
    - Highly effective when used at appropriate dosing for weight.
    - Off-label indication but widely used for scabies.
    - Published clinical data in young children are limited.
    - 2 doses, separated by ~1–2 weeks, may be necessary.
- All potentially infested items should be washed immediately after treatment of all individuals in the same household.
  - Minimum of 65°C (149°F) for minimum of 15 minutes (preferably ≥30 minutes)
    - Clothing
    - Bedding
    - Combs
    - Towels
- Pruritus and rash.
  - Often persist for ≥2–4 weeks after successful eradication of an infestation.
    - Treatment should be repeated only when continued infestation with live mites is clearly demonstrated.
  - Pruritus can be treated with oral antihistamines or mild topical agents, such as emollients, pramoxine, or very minimal concentrations of menthol.
  - Nodular scabies, post-scabetic nodules.
    - Hypersensitivity reaction
    - Red to purple discrete nodules up to 2 cm in diameter on surfaces usually covered by clothing
    - Usually on the genitals or around the axillae
    - Usually respond to topical or intralesional injections of corticosteroids

WHEN TO ADMIT

- The patient has severe systemic allergic reactions to insect bites.
- The patient needs intravenous antibiotics to treat secondary bacterial infection, cellulitis, or systemic infection.
- The patient develops noninfectious complications, such as
  - Acute postinfectious glomerulonephritis
  - Hypertension
- Patient is suspected of having contracted
  - Viral meningitis
  - Other severe or systemic illness through insect bites

WHEN TO REFER

- Refer to an allergist if
  - The patient develops a severe allergic reaction to insect bites, especially repeatedly.
  - Hymenoptera allergy is suspected.
- Refer to a dermatologist if
  - Scabies are suspected and there is risk for contagion within an institutional setting.
  - Suspected infestation is unresponsive to treatment.
  - Other persistent itching erupts.

COMPLICATIONS

Insect Bites

- Infection
  - Impetigo
  - Cellulitis
- Eczematous changes
  - Inflamed plaques
    - From scratching
    - From topical remedies that cause irritant or allergic contact dermatitis (eg, neomycin)
- Localized hypersensitivity reactions
  - Papular urticaria
    - Recurrent crops of urticarial (hive-like) papules, nodules, or wheals on exposed surfaces; may be new or reactivated old bites.
    - Occurs in some sensitized individuals.
    - Can last weeks or months.
    - The patient experiences profound itch, especially if repeatedly scratched or otherwise traumatized.
    - Scratching can leave scarring or postinflammatory pigment change, most often hyperpigmentation.
- Systemic reactions
  - Viral encephalitis or tick-borne disease
    - More thorough follow-up
    - Consideration of hospital observation
  - Bacterial infection
    - Can lead to cellulitis or a multitude of toxin-induced or immune-mediated complications, such as nephritis

Infestation

- Bacterial infection.
  - Toxin-producing strains
- Cellulitis.
- Systemic treatment may be necessary.
  - Especially in immunosuppressed children.
  - Attention must be given to the potential for long-term sequela of bacterial infection, such as nephritis.

PREVENTION

- Insect bites
  - Cover as much of the body as possible with clothing.
  - Judicious use of repellents.
    - Picaridin.
    - N,N-diethyl-m-toluamide (DEET) at exposed areas (avoiding children's hands, eyes, and mouth areas).
    - DEET can cause central nervous system and systemic symptoms in children.
    - DEET is usually safe to use intermittently and in moderation at concentrations ≤30% in infants and children >2 months.
    - Alternate repellents, such as lemon eucalyptus, are less toxic but may be less effective.
  - For mosquitoes, avoid potential attractants, such as bright clothing.
  - Use of bed nets (especially for infants) and by judicious, careful use of repellents.
- Infestation
  - Pediculosis
    - No-nit policies aimed at excluding children from school are ineffective.
    - Such policies penalize children excessively by causing missed school days.

DEFINITION

- *Intellectual disability* is the preferred synonym for mental retardation.
  - In 2010, the US Congress passed Rosa's law, making *intellectual disability* the new legal definition for the diagnosis formerly known as *mental retardation*.
  - In 2013, the American Psychiatric Association changed the diagnosis to *intellectual disability* (*intellectual developmental disorder*).
  - Therefore, primary care physicians and others should use the term *intellectual disability* to assist patients in obtaining appropriate supports.
- American Association on Intellectual and Developmental Disabilities (AAIDD) guidelines for the accurate use of the term *intellectual disability.*
  - The level of functioning of an individual should be considered within her particular social and cultural context.
  - Any assessment of cognitive and adaptive ability should take into account communication, sensory, motor, and behavioral functioning.
  - An individual's strengths must be emphasized in assessments and included in support plans.
  - The purpose of assessing limitations is to guide the development of appropriate supports for the individual in question.
  - The provision of individualized supports is expected to improve functioning significantly.
- The AAIDD defines *intellectual disability* as impairments in cognitive functioning and adaptive behavior that develop <18 years.
  - *Cognitive impairment* is defined as performance in the abnormally low range on standard assessments of intelligence.
    - Cognitive impairment implies significantly low scores in all domains of intelligence testing.
    - Widely discrepant scores in various domains would be best defined as *learning disability,* not intellectual disability.
  - *Adaptive impairment* is defined by functioning in the abnormally low range on formal measures of adaptive functioning (eg, Vineland Adaptive Behavior Scales).
    - Includes such domains as communication, self-care, home living, social or interpersonal skills, ability to use community resources, self-direction, functional academic skills, work, leisure, health, and safety
- Implicit is the understanding that, although cognitive and adaptive impairments are not reversible, intellectual disability can be ameliorated by environmental modifications and supports.
- *Developmental delay* reflects functioning significantly behind expectations for chronologic age in a particular developmental domain.
  - Some children experience developmental delay in a single domain, whereas others have delays in multiple or all domains.
  - This term is often perceived by parents and laypersons to suggest that the child will, at some time, make up the delay.
    - Catch-up frequently occurs in the case of delays in isolated domains.
    - The child who is delayed in all domains, frequently described as having *global developmental delay,* is less likely to catch up.
  - In general, professionals are hesitant to describe children as having intellectual disability until they are approximately at the age of school entry.
    - This hesitation allows parents to focus on interventions that maximize the child's potential while de-emphasizing what the child cannot accomplish.
    - On the other hand, professionals and laypersons alike often continue to use the term *developmental delay* far beyond the time when there is any uncertainly in diagnosis, well into the school years, and defer the use of intellectual disability excessively.

SIGNS AND SYMPTOMS

Intellectual Disability by Level of Function

- Mild
  - IQ: 55–70.
  - 5th-grade academics by 18 years of age.
  - Support level: intermittent.
  - Adults generally function well independently, are able to work in competitive employment, and manage domestic affairs adequately.
  - Individuals may have difficulty with stress.
  - Individuals with mild intellectual disability usually benefit from the intermittent support of a care coordinator.
- Moderate
  - IQ: 40–55.
  - 2nd-grade academics by 18 years of age.
  - Support level: limited.
  - Most adults are able to work in the community but often require ongoing job coaching, particularly to cope with changes in routine.

- Adults are typically able to manage many aspects of their domestic life, such as hygiene and taking public transportation, but require some assistance with daily living.

- Severe
  - IQ: 25–40.
  - Preschool academics by 18 years of age.
  - Support level: extensive.
  - Individuals with severe intellectual disability typically cannot work in the community.
  - Individuals often require significant daily assistance with many aspects of their domestic life.
- Profound
  - IQ: <25.
  - Support level: pervasive.
  - Individuals with profound intellectual disability cannot work in the community.
  - Individuals require significant daily assistance with many aspects of their domestic life.

Physical Examination

- Can provide important clues to the cause of intellectual disability.
- In the workup of global developmental delay or intellectual disability, referral for assessment of hearing and vision may be important.
- In addition to determining potential causes of intellectual disability, physical examination
  - Establishes a connection with the child
  - Aids in assessment of interpersonal interactions

Behavioral Symptoms

- Avoidance of diagnostic "overshadowing" or attributing all symptoms to intellectual disability is important.
  - Autism spectrum disorder (ASD) is a common comorbid feature of intellectual disability.
    - Several behavioral symptoms, such as irritability, aggression, and self-injury, are seen in intellectual disability and ASD.
    - ASD occurs at a higher rate in individuals with intellectual disability; a diagnosis of ASD prompts differences in management.
    - For this reason, specialists strongly recommend that ASD be considered, particularly in the face of characteristic symptoms.
  - Irritability and aggression have long been seen as intrinsic features of intellectual disability, often precluding more meticulous investigation.
    - Frequently, they are symptoms of psychiatric illness, such as depression or anxiety.
  - Self-injury may be a sign of physical illness.
    - For example, hitting the chest may be an indication of undiagnosed gastroesophageal reflux.
  - Apparent hypersexuality may be a manifestation of an uncomfortable erection in the context of inadequate sexuality education.

Nonspecific Dysmorphic Features Associated With Anomalous Brain Development

- Microcephaly
  - Reduced brain growth
- Cranial asymmetry
  - Premature suture fusion versus deforming external forces versus abnormal underlying brain growth
- Hair: absent or multiple (>2) parietal whorls
  - Abnormal brain development between 10 and 16 weeks' gestation
- *Cowlick,* or anterior upsweep of scalp hair
  - Posterior displacement of junction of parietal and frontal hair streams, resulting from reduced frontal brain development
- Short palpebral fissures
  - Deficient frontal brain growth
- Up-slanted palpebral fissures
  - Relatively deficient frontal brain growth compared with midface
- Low-set ears (top of helix below outer canthi)
  - Reflects delayed morphogenesis, as ears are low set in the early fetus
- Posterior rotation of ears (axis tilted backward >15°)
  - Reflects delayed morphogenesis, as ears are posteriorly rotated in the early fetus
- High-arched mouth
  - Persistent lateral palatal ridges, indicative of oral hypotonia or other oral-motor dysfunction

DIFFERENTIAL DIAGNOSIS

Syndromes Associated With Intellectual Disability

- Down syndrome (trisomy 21)
  - Brachycephaly
  - Microcephaly
  - Epicanthal folds
  - Brushfield spots
  - Up-slanting palpebral fissures
  - Small ears
  - Small nose with low nasal bridge

- Brachydactyly and clinodactyly
- Single transverse palmar crease
- Wide gap and plantar crease between first and second toes
- Hypotonia
- Short stature

- Fragile X syndrome
  - High forehead
  - Long jaw or face
  - Large protuberant ears
  - Velvety palmar skin with dorsal redundancy
  - Hyperextensible joints
  - Peri-pubertal macroorchidism
  - Early onset overgrowth
  - Initial shyness
  - Repetitive behaviors and stereotypies
- Fetal alcohol syndrome
  - Microcephaly
  - Short palpebral fissures
  - Maxillary hypoplasia
  - Flat philtrum
  - Thin upper lip
  - Small distal phalanges and small fifth fingernail
  - Joint anomalies of position and function
  - Short stature
- Williams syndrome
  - Stellate iris
  - Short palpebral fissures
  - Medial eyebrow flare
  - Periorbital fullness
  - Flat nasal bridge
  - Anteverted nares
  - Long philtrum
  - Prominent lips
  - Hoarse voice
  - Heart murmur
  - Hyperactive deep-tendon reflexes
  - Friendly personality
  - Hyperactivity
  - Short stature
- Velocardiofacial syndrome
  - Narrow palpebral fissures
  - Cleft palate
  - Velopharyngeal insufficiency
  - Prominent nose with narrow base
  - Abundant scalp hair
  - Long face
  - Retruded mandible
  - Heart murmur
  - Slender, hypotonic limbs with hyperextensible hands and fingers
- Rett syndrome
  - Acquired delay in head growth
  - Acquired diminished eye contact and loss of speech
  - Repetitive purposeless midline hand movements, such as wringing or washing
  - Apraxia
  - Hypotonia, principally in girls

Neurocutaneous Findings Associated With Intellectual Disability

- Tuberous sclerosis complex
  - Hypomelanotic macules
    - Oval or ash-leaf shaped, few millimeters to centimeters, mostly on trunk or extremities; may occur in infancy
  - Shagreen patches
    - Firm yellow to red clusters of nodules, few millimeters to centimeters, on dorsum of body, particularly lumbosacral area; typically occurring at puberty (less commonly before)
  - Facial angiofibroma
    - Pink or red shiny nodules, on face, especially on nasolabial folds, usually appearing between 2 and 5 years of age
  - Forehead fibrous plaque
    - Yellowish-brown or flesh-colored, raised soft or hard plaque, few millimeters to centimeters, on forehead or scalp; can occur at any age
  - Periungual fibroma
    - Reddish or flesh colored, arising from nail bed or cuticle, found on toes more often than fingers, usually occurring at puberty or later
- Neurofibromatosis
  - Café au lait spots
    - Usually hyperpigmented but also includes hypopigmented macules ≥5 mm
    - Axillary freckling
      - Small brown macules in axillae and perineum
    - Cutaneous neurofibroma
      - Small, raised, soft, pigmented nodules
- Sturge-Weber syndrome
  - Cranial port-wine stain
    - Light pink to deep purple birthmark, typically involving at least one upper eyelid and the forehead

DIAGNOSTIC APPROACH

General

- Diagnosis of intellectual disability requires documentation of impairment of cognition and adaptive functioning.
- Communicating with families and patients about diagnosis is challenging.
  - Thoughtful communication is essential in helping families acknowledge a diagnosis that is difficult to accept.
  - Readying the family to access communication requires careful and specific use of diagnostic labels, and the consistent use of person-first language shows respect and compassion.
    - To state impairment first, as in "the intellectually disabled child," implies that disability is the most salient characteristic of the child.
    - Saying "the child with an intellectual disability" is preferable.
- The American Academy of Neurology has established diagnostic criteria for intellectual disability; these may be used for the diagnostic workup of intellectual disability and global developmental delay.
- A useful framework for organizing the collection of these data, and for organizing the care plan, is provided by the International Classification of Functioning, Disability, and Health (ICF).
  - Emphasis on function over diagnostic labels and consideration of environmental factors.
  - Congruent with guidelines put forth by the AAIDD.
  - For the primary care physician, the ICF can serve as a review of functional status.
- International classification of functioning to organize evaluation and care plan.

Criteria for Diagnosis of Intellectual Disability

- Cognitive impairment
  - IQ ≥2 standard deviations (SDs) of 15 below a mean of 100 (IQ ≤70)
- Adaptive impairment
  - Adaptive skills include such domains as communication, self-care, home living, social or interpersonal skills, use of community resources, self-direction, functional academic skills, work, leisure, health, and safety.
  - Adaptive impairment is identified by functioning in the range of impairment in these areas.
    - ≥2 SDs below the mean in these areas, as measured by formal testing of adaptive functioning, such as the Vineland Adaptive Behavior Scales
- Onset of cognitive and adaptive impairment during the developmental period (usually <18 years)
  - Onset of cognitive and adaptive impairment after the developmental period would be referred to by etiology (eg, as traumatic brain injury).

ICF Guidelines to Evaluation

- Learning and applying knowledge
  - Elements to include in evaluation: learning, thinking, problem-solving, and decision-making
- General tasks and demands
  - Elements to include in evaluation: carrying out tasks, organizing routines, handling stress
- Communication
  - Elements to include in evaluation: use of language, signs, and symbols; receiving and producing messages; carrying on conversation; use of communication devices and techniques
- Mobility
  - Elements to include in evaluation: moving body position or location; transferring from one place to another; carrying, moving, and manipulating objects; walking, running, climbing; using transportation
- Self-care
  - Elements to include in evaluation: washing, dressing, grooming, eating, drinking, hygiene, health practices
- Domestic life
  - Elements to include in evaluation: acquiring food, clothing, place to live; household chores; assisting others
- Interpersonal interactions and relationships
  - Elements to include in evaluation: basic and complex interactions with people, including strangers, friends, relatives, immediate family members, and intimate relations in a socially appropriate manner
- Major life areas
  - Elements to include in evaluation: carrying out tasks related to education, work, and economic transactions
- Community, social, and civic life
  - Elements to include in evaluation: recreation and leisure, religion or spirituality, political life or citizenship

LABORATORY FINDINGS

- Karyotype
  - Recommended in all children with moderate to severe global developmental delay or intellectual disability
- Metabolic workup
  - Not generally recommended if newborn screen is documented
  - Recommended with specific family history, consanguinity, regression, or episodic decompensation
- Fragile X syndrome (DNA methylation testing)
  - Recommended in boys with moderate to severe global developmental delay or intellectual disability
  - Particularly recommended when characteristic features are present
- Rett syndrome (*MECP2* gene testing)
  - Recommended in girls with moderate to severe global developmental delay or intellectual disability
  - Particularly recommended when characteristic features are present
- Subtelomeric fluorescence in situ hybridization
  - Before the development of complete genomic hybridization technology, this was the best test for the detection of small subtelomeric rearrangements.
  - This test has been replaced by microarray comparative genomic hybridization.
- Microarray comparative genomic hybridization
  - Consider in moderate to severe global developmental delay or intellectual disability.
  - This test has higher yield when ≥1 of the following features are present:
    - Family history of unexplained moderate to severe intellectual disability
    - Prenatal onset growth retardation
    - Postnatal growth abnormalities, including microcephaly or macrocephaly or tall or short stature
    - ≥2 dysmorphic facial features or non-facial congenital anomalies
- Thyroid function testing
  - Recommended if no newborn screen documented or with characteristic symptoms, such as
    - Late tooth eruption or fontanel closure
    - Weight for age above height for age
    - Constipation
    - Delayed relaxation phase of deep-tendon reflexes
- Lead testing
  - Levels are found to be elevated at a higher rate in children with intellectual disability than in children without.
  - Pica is a behavioral characteristic associated with intellectual disability.

IMAGING

- Brain magnetic resonance imaging
  - Recommended for global developmental delay, although clinical picture should be taken into account
  - Lower yield in mild global developmental delay, which tends to be familial
  - Higher yield with focal or abnormal neurological examination, in the presence of cranial anomalies or neurocutaneous features

DIAGNOSTIC PROCEDURES

- Ophthalmologic assessment
  - Recommended in all children with moderate to severe global developmental delay or intellectual disability
- Audiologic assessment
  - Recommended in all children with moderate to severe global developmental delay or intellectual disability
- Electroencephalography
  - Recommended only if a clinical indication of seizures is present

WHEN TO REFER

- Infants and toddlers failing to meet developmental milestones using standard screening and surveillance instruments, such as
  - Ages & Stages Questionnaire
  - Child Development Inventory
  - *Bright Futures Guidelines*
- A pediatrician need not conduct formal developmental screening to refer for evaluation through early intervention (EI) programs.
- Referrals can be based on objective criteria or clinical judgment.
- Parents who express concerns about their child's development should have their concerns validated by a referral to EI services.
- If the primary care physician even suspects developmental delay, erring on the side of caution would be advisable.

- Children with a new diagnosis of global developmental delay or of intellectual disability
  - Should have a complete medical evaluation to determine the causes of the delays.
  - The primary care physician may wish to refer to subspecialists in genetics, neurology, developmental and behavioral pediatrics, or neurodevelopmental disabilities.
- Children of sufficient age who are suspected of having intellectual disability and who have not had a formal psychological assessment should be referred for evaluation of cognitive abilities, academic achievement, and adaptive skills.
  - Families may obtain such testing free of charge through their local school district by making a formal request for a multidisciplinary evaluation.
  - Primary care physicians can support families in this endeavor by providing references to the process of requesting an evaluation through the school district.
  - Families may obtain an independent psychological evaluation from a private pediatric psychologist or pediatric neuropsychologist.

Iron Deficiency Anemia

DEFINITION

- Iron deficiency occurs when total body iron content is diminished.
- When absorption exceeds losses, iron surplus is stored in the reticuloendothelial system.
  - Liver
  - Spleen
  - Bone marrow
- Iron is removed from the reticuloendothelial storage pool to compensate for negative iron balance.
- Development of iron deficiency proceeds through a series of 3 overlapping stages.
- Stage 1.
  - Storage iron depletion.
  - Anisocytosis and an increased percentage of microcytic cells are the first hematologic abnormalities.
  - During this stage, there is no deficit of iron supplied to the erythroid marrow for red blood cell (RBC) production.
  - The decrease in body iron stores is typically measured by serum ferritin.
- Stage 2.
  - If the negative iron balance continues, iron-deficient erythropoiesis (IDE) will occur.
  - Mean corpuscular volume (MCV) and mean corpuscular hemoglobin (Hb) (MCHC) decline.
  - Erythroid iron supply is diminished, but Hb concentration remains in the reference range.
  - Serum transferrin saturation is increased in the first or second stage of iron deficiency.
  - Soluble transferrin receptors (sTfRs) are increased, zinc protoporphyrin (ZnPP) is increased, and reticulocyte Hb concentration (CHr) is decreased.
- Stage 3.
  - If the negative iron balance persists, iron deficiency anemia (IDA) finally develops.
  - Stage is characterized by a decrease in the Hb concentration and reduction in RBC size and Hb content.
  - Hematologic abnormalities in iron deficiency progress as there is progressive impairment of hematopoiesis.
  - Low MCHC and low Hb concentration.
- Prevention of IDA in early childhood is an important public health issue.
  - IDA is the most common nutritional deficiency worldwide.

SIGNS AND SYMPTOMS

History

- The onset and progression of iron deficiency are usually gradual.
- Most children will not have major symptoms.
- Iron deficiency in infants and children is associated with
  - Generalized weakness
  - Irritability
  - Easy fatigability
  - Headaches
  - Poor feeding
  - Anorexia
  - Pica
  - Poor weight gain

Physical Examination

- The physical examination is usually unremarkable except for marked pallor of the mucous membranes and skin.
- Other physical findings associated with IDA but rarely observed include
  - Mild hepatosplenomegaly
  - Lymphadenopathy
  - Glossitis
  - Stomatitis
  - Blue sclerae
  - Koilonychia (spoon-shaped nails)
- Most mild cases of IDA do not include pallor.

DIFFERENTIAL DIAGNOSIS

- Iron deficiency must be distinguished from other hypochromic microcytic anemias.
- Serum transferrin receptor levels help discriminate iron deficiency from the anemia of inflammation or chronic disease.

Thalassemia Trait

- IDA and thalassemia trait are the most common causes of mild microcytic anemia with Hb level ≥9 g/dL.
- The RBC count is often increased above normal despite the presence of a mild anemia and microcytosis in thalassemia trait, whereas it is reduced in IDA.
- The RBC distribution width (RDW) is increased in iron deficiency.

- The Mentzer index, defined as the MCV divided by the RBC count in millions, can help distinguish the anemia of iron deficiency from that of β-thalassemia trait.
  - In IDA, the Mentzer index is often >13.5.
  - In β-thalassemia trait, it is <11.5, with 82% specificity.
  - The RDW index (RDWI) is calculated using the formula RDWI = (MCV / RBC × RDW)
    - An RDWI ≥220 is indicative of IDA.
    - An RDWI <220 is indicative of thalassemia trait, with a specificity of 92%.
- The RBC count and RDWI are the most reliable discrimination indices in differentiating between β-thalassemia trait and IDA.
- If α- and β-thalassemia trait or HbE disease is suspected, the diagnosis can be established by
  - Review of the newborn screen.
  - Performing Hb electrophoresis (only in case of β-thalassemia and not α-thalassemia).
    - Electrophoretic methods can be diagnostic in the case of β-thalassemia or HbE but may not be informative in thalassemia beyond infancy.
    - Because thalassemia trait is frequently not associated with a Hb level <9 g/dL, it is not included in the differential diagnosis in severe anemia.
  - Patients who are double heterozygotes for β-thalassemia and HbE may have moderate to severe anemia.
  - The diagnosis of α-thalassemia trait can be assumed when a patient with a familial hypochromic microcytic anemia has normal results of iron studies (including ferritin), reference levels of HbA_2 and HbF, and normal Hb electrophoresis.
  - It is a diagnosis of exclusion, except in the newborn period, when neonates with α-thalassemia trait have 3%–10% Hb Bart's (γ_4), which may be detected in the newborn screen if there is a mutation involving the deletion or loss of function of ≥1 of the α-globin genes.

HbH Disease

- HbH disease, another form of α-thalassemia, results from deletion of 3 of the 4 α-globin genes.
- It is characterized by hypochromia and microcytosis.
- A mild hemolytic component is present from instability of the β-chain tetramers (HbH) resulting from a deficiency of α-globin chains.
- Beyond infancy, HbH is readily identified by Hb electrophoresis.
- During the newborn period, the moderately severe α-globin deficiency allows accumulation of more γ chains, and the concentration of Hb Bart's is >20%.

Anemia of Chronic Disease or Inflammation

- Inflammation impairs the supply of iron to the plasma and ultimately results in a form of anemia called *anemia of chronic disease* or *anemia of inflammation*.
  - It is usually normocytic, although it may occasionally be slightly microcytic.
  - Because inflammation alters screening tests for iron status in the same manner as true iron deficiency, the distinction between anemia of chronic disease and IDA requires tissue-related iron measurements.
  - Usefulness of the serum ferritin in the diagnosis of IDA is compromised by the effect of inflammation on the value.
  - Consequently, a serum ferritin concentration >30 mg/L in an anemic patient does not exclude IDA in the presence of chronic inflammation.
  - However, because specificity for iron deficiency falls sharply with increasing ferritin levels, there is considerable overlap between iron-deficient and iron-replete patients, and ferritin levels between 20 and 100 mcg/L are often inconclusive, whereas serum ferritin levels >100 mcg/L usually exclude iron deficiency.
- C-reactive protein (CRP) level is generally considered to be the best laboratory marker of inflammation.
  - If CRP is <30 mg/L, it is generally considered unlikely that the inflammation is sufficient to increase the serum ferritin level.
  - Suggested ferritin levels of <40 mg/L and <70 mg/L are used to diagnose IDA in anemic patients without and with inflammation, respectively.
  - The sTfR measurement for identifying IDA is one in which the concentration is not affected by inflammation.
  - Use of an sTfR to ferritin ratio >1.70 further improves the specificity of the diagnosis of IDA and may eliminate the need for bone marrow examination for assessment of iron stores.

Lead Poisoning and Anemia

- Lead poisoning and IDA are associated with high levels of RBC ZnPP.
- Iron deficiency and lead poisoning frequently coexist.
- Although the nature of their relationship is not completely elucidated, characterization of a common iron-lead transporter and epidemiologic studies among children strongly suggest that iron deficiency may increase susceptibility to lead poisoning.
- In cases of lead poisoning associated with iron deficiency, the RBCs are morphologically similar, but coarse basophilic stippling of the RBCs is frequently prominent.
- Increases in blood lead, ZnPP to heme (ZnPP:H) ratio, and urinary coproporphyrin levels are seen.

DIAGNOSTIC APPROACH

- Diagnosis of IDA is made by the combination of
  - RBC indices
  - Serum transferrin saturation
  - Ferritin
- Transferrin saturation and ferritin may be altered by
  - Infection
  - Inflammation
  - Cancer
  - Starvation
- Although absence of iron stores in the bone marrow remains the gold standard for a diagnosis of IDA, this test is rarely used because of patient discomfort and the difficulty of standardizing bone marrow iron stain.
- Once IDA is diagnosed, efforts should be undertaken to establish its cause.
- A therapeutic iron trial has been proposed as a convenient method to diagnose iron deficiency in patients with anemia.
  - This approach is reasonable in otherwise healthy individuals.
  - Making a definitive laboratory diagnosis at the outset is preferable for those at high risk of deficiency, such as
    - Infants
    - Teenaged girls
    - Pregnant women

LABORATORY FINDINGS

- Specific laboratory findings are associated with each of the 3 stages of iron deficiency (**Table 1**).
- Tests demonstrate a reduced supply of plasma iron or poor hemoglobinization of circulating RBCs.
- Definitive tests identify IDA by measuring iron-related proteins derived from the iron storage compartment in macrophages or the iron utilization compartment in RBC precursors.

Screening Measurements

Hb Concentration

- The most commonly used screening test for iron deficiency is relatively insensitive because an individual with normal body iron stores must lose a large portion of body iron before Hb falls below laboratory definitions of anemia.
- Low Hb does not distinguish among the causes of anemia other than iron deficiency, so additional testing is required.

Serum Iron and Transferrin Saturation

- Serum iron levels normally fluctuate daily, with maximal levels occurring in the morning and minimal levels in the evening.
- Total iron-binding capacity (TIBC) varies less than serum iron but is harder to measure accurately.
- Reference TIBC is 250–400 mg/dL, but as serum iron levels decrease, TIBC increases to ≥450 mg/dL.
- Iron and TIBC measurements are useful in distinguishing IDA from anemia of chronic disease.
- Serum iron levels decrease with both, but TIBC levels also decrease in chronic disease states (**Table 2**).
- Degree of iron saturation of plasma transferrin is calculated as follows: transferrin saturation = (serum iron concentration / TIBC) × 100.
- Serum iron and TIBC levels help confirm the diagnosis of iron deficiency, with a low serum iron and a high transferrin level, resulting in a transferrin saturation <10%–15%.
- Transferrin levels are increased in iron-deficiency states because of increased hepatic synthesis of the protein and greater liberation of apotransferrin (the transport protein without iron) from Hb-synthesizing sites.
- This relatively inexpensive measurement is widely available.
- Marked diurnal variation in plasma iron values and numerous clinical disorders that affect transferrin saturation limit its use in the clinical setting.
- Transferrin saturation.
  - Reference or high transferrin saturation is useful for excluding IDA.
  - Low transferrin saturation is useful for identifying IDA.

Table 1. Laboratory Abnormalities in the 3 Stages of Iron Deficiency

Stage	Description
I: Iron depletion	• Serum ferritin ↓ • Bone marrow iron ↓
II: Iron-deficient erythropoiesis	• Serum ferritin ↓ • Bone marrow iron ↓ • Serum iron ↓ • TIBC ↑
III: Iron deficiency anemia	• Serum ferritin ↓ • Bone marrow iron ↓ • Serum iron ↓ • TIBC ↑ • Hemoglobin ↓ • Hematocrit ↓ • MCV ↓ • RDW ↑

I

↑ Indicates increased; ↓, decreased

Abbreviations: MCV, mean corpuscular volume; RDW, red blood cell distribution width; TIBC, total iron-binding capacity.

From Roper D, Stein S, Payne M, Coleman M. Anemias caused by impaired production of erythrocytes. In: Rodak BF, ed. *Diagnostic Hematology.* Philadelphia, PA: WB Saunders; 1995. Reprinted by permission.

Table 2. Laboratory Findings Associated With the Differential Diagnosis of Microcytic Anemias

Finding	Iron Deficiency	Lead Poisoning	β-Thalassemia Trait	Chronic Disease
Ferritin	↓	Normal	Normal	↑
Serum iron	↓	Normal	Normal	↑
Total iron-binding capacity	↑	Normal	Normal	↓
Erythrocyte zinc protoporphyrin	↑	↑↑	Normal	↑
Red blood cell distribution width	↑	Normal	Normal	Normal
Serum transferrin receptor	↑	Normal	↑	Normal

↑, increased; ↑↑, very increased; ↓, decreased. Iron deficiency and lead poisoning frequently coexist.

- Among other conditions, pregnancy and oral contraceptives may be associated with elevated transferrin level and transferrin saturation, thus complicating the diagnosis of IDA.
  - In these situations, combination of laboratory studies, such as serum ferritin and sTfR, may be useful in the diagnosis of iron deficiency.

RBC Indexes

- Development of electronic counters has made use of RBC indexes widely available for initial screening of infants and children.
- These tests are highly reproducible and less subject to sampling error compared with Hb determinations because tissue fluid dilution does not affect RBC size.

- RBCs become smaller than normal with decreased MCV, and their Hb content decreases with decreased MCHC.
- RDW approximates the standard deviation of the RBC size variation.
- Normal RDWs occur in the range of 12%–17%.
- In IDA, a marked dispersion exists in cell volumes (sizes), such that the RDW increases.
- RBC indexes in infancy and childhood are described in **Table 3.**

ZnPP

- A simple and reliable measurement of IDE is the RBC ZnPP, a product of abnormal heme synthesis.
- Normally, a trace of zinc rather than iron is incorporated into protoporphyrin during the final step of heme biosynthesis.
- In states of IDE, ZnPP formation is enhanced.
- An increase in the ZnPP:H ratio >80 mmol/mol is a sensitive, specific, and cost-effective test for identifying pre-anemic iron deficiency.
- A major advantage is the ability to measure the ZnPP:H ratio directly on a drop of blood using a portable instrument called a *hematofluorometer*.
- Initially, ZnPP was erroneously characterized as metal-free protoporphyrin or free RBC protoporphyrin or RBC protoporphyrin.
- Now, most presumed metal-free protoporphyrin in RBCs is known to be largely an artifact of older analytic procedures (still used in some laboratories).
- Because ~95% of the nonheme protoporphyrin in RBCs is ZnPP, this procedure should not create a diagnostic problem.
- The ZnPP:H ratio is an indicator of iron available to developing RBCs in bone marrow regardless of the cause, such as iron deficiency, inflammation, or functional iron deficiency, such as in chronic renal failure.
- Another significant limitation of ZnPP is with lead toxicity and the reference range with environmental lead exposure, infections, inflammatory diseases, and protoporphyria.
- However, the ZnPP:H ratio is not increased in thalassemia trait, which makes ZnPP:H ratio determinations helpful in distinguishing iron deficiency from α- or β-thalassemia trait, in addition to its role in screening for iron deficiency (**Table 2**).

Reticulocyte Hb

- The mean reticulocyte Hb content is analogous to the RBC MCHC but with the advantage of monitoring hemoglobinization of the most recently produced RBCs.
- A CHr <26 pg is an early indicator of iron-restricted hematopoiesis and IDA in children.
- Median reticulocyte Hb was 2.0 fmol in the non–iron-deficient patient group and 1.5 fmol in the iron-deficient patient group ($P < .01$), with overlap between 1.2 and 2.2 fmol, which includes 90% of the data.

I

Table 3. Red Blood Cell Indexes During Infancy and Childhood

Age	Hemoglobin (g/dL)		Hematocrit (%)		Reticulocytes (%)	MCV (fL)
	Mean	Range	Mean	Range	Mean	Lowest
Child						
Cord blood	16.8	13.7–20.1	55	45–65	5.0	110
2 wk	16.5	13.0–20.0	50	42–66	1.0	107
3 mo	12.0	9.5–14.5	36	31–41	1.0	80
6 mo–6 y	12.0	10.5–14.0	37	33–42	1.0	70–74
7–12 y	13.0	11.0–16.0	38	34–40	1.0	76–80
Adult						
Female	14	12.0–16.0	42	37–47	1.6	80
Male	16	14.0–18.0	47	42–52	1.6	80

Abbreviation: MCV, mean corpuscular volume.

Modified from Behrman RE. *Nelson Textbook of Pediatrics.* 17th ed. Philadelphia, PA: WB Saunders; 2004. Copyright © 2004, Elsevier, with permission.

- Median sTfR was 6.4 mg/L in the iron-deficient group and 3.3 mg/L in the non–iron-deficient group (P <.01), with 27% of the data falling into the overlapping interval of 4.6–14.5 mg/L.
- The diagnostic power of reticulocyte Hb is limited in patients with high MCV or with RBC disorders, such as thalassemia.

Peripheral Blood Smear

- Examination of the blood smear in IDA reveals
  - Hypochromic microcytes
  - Poikilocytes
  - Elliptocytes
  - Target cells
- Presence of basophilic stippling suggests associated lead poisoning.
- RBC changes seen on the blood smear are not specific for iron deficiency.
- Leukocyte count and morphology in IDA are usually normal.
- Thrombocytosis and thrombocytopenia occur with iron deficiency.
  - Thrombocytopenia is more common in severe iron deficiency and resolves once iron therapy is begun.

Definitive Tests

- Absence of stainable iron in bone marrow is a definitive test for IDA but is not routinely applicable for obvious reasons, and the bone marrow iron stain must be performed in standard conditions to be reliable.
- The 2 key definitive measurements for diagnosing iron deficiency are the serum ferritin and the serum transferrin receptor.
  - Serum ferritin reflects body iron stores in healthy individuals.
    - Definitive serum ferritin levels vary with age during infancy and childhood.
    - Ferritin is an acute-phase reactant.
    - Serum ferritin levels are increased during infections, inflammatory processes, and liver disease.
    - Although low serum ferritin is diagnostic of iron deficiency, high ferritin associated with inflammation or liver disease does not rule out concomitant iron deficiency.
    - In children <5 years, serum ferritin levels <12 mcg/L and <30 mcg/L in the presence of infection indicate iron deficiency.
    - In children >5 years, serum ferritin <15 mcg/L indicates iron deficiency.
  - sTfR directly correlates with total mass of erythroid precursor.
    - Proteolytic cleavage of transferrin receptors can be measured in serum as sTfR.
    - sTfR is high in iron deficiency and in conditions resulting in increased production of RBCs, including thalassemia and sickle cell disease.
    - Because sTfR is not affected by inflammation, it is useful in distinguishing iron deficiency from chronic inflammatory states that do not have high sTfR (see **Table 2**).
    - Infants have higher baseline sTfR levels than children and adults, indicating the need to establish age-specific reference values.
    - The ratio of sTfR to serum ferritin has been shown to have excellent performance in estimating body iron stores but is limited by lack of standardization.
    - Use of the sTfR to log ferritin ratio >1.70 improves the specificity of the diagnosis of IDA.

Bone Marrow Iron

- Normal bone marrow aspirate stained with Prussian blue reveals the presence of iron in RBC precursors (normoblasts) and serves as a reliable index of body iron stores.
- In iron deficiency, the number of iron granules in normoblasts is decreased, and stainable iron in the marrow aspirate is almost completely absent.
- Almost never needed to establish a diagnosis of iron deficiency.

Diagnosis of Iron Deficiency, IDA, and the Underlying Cause

- Hb, the most commonly used screening test for IDA, is limited by the fact that anemia does not occur until there is marked depletion of storage iron and progression of iron-restricted erythropoiesis.
- Serum ferritin is limited by the fact that it is an acute phase reactant.
- sTfR, a marker of tissue iron deficiency, is not decreased until there is substantial iron-restricted erythropoiesis.
- Thus, in the absence of inflammation, in healthy populations in high-resource countries with low incidence of IDA, serum ferritin remains the most useful screening test for iron deficiency without anemia.

- Microcytic anemia can result from a number of causes, and every effort must be made to establish or exclude diagnosis of IDA and to determine the underlying cause.
- Because no single clinical finding or laboratory test is diagnostic of iron deficiency, a combination of available clinical findings and laboratory data must be considered to establish iron deficiency caused by inflammation.
- CHr can distinguish between IDA and anemia related to hemoglobinopathy trait.

TREATMENT APPROACH

- The treatment of choice for iron deficiency is oral administration of iron.

SPECIFIC TREATMENTS

Oral Iron

- Although various iron salts are available, ferrous sulfate is inexpensive and well tolerated, although adverse effects may occur, such as
  - Nausea
  - Dyspepsia
  - Constipation
  - Diarrhea
- After diagnosis is confirmed, by a response to a therapeutic trial or further tests, oral therapy with elemental iron at 3–6 mg/kg per day should be continued for 2–3 months after normal Hb levels have been restored.
- To control adverse effects
  - Administer with or immediately after meals.
  - Reductions in the amount of iron in each dose or reduction in frequency to a single daily dose may help.
  - If intolerance is persistent, switching to ferrous gluconate may be helpful.
- Iron polysaccharide complex has the advantage of being available as tablets or elixir and is well tolerated.
- Absorption.
  - About twice as much iron is absorbed on an empty stomach as at mealtime.
  - Consumption of milk should be limited to allow increased intake of iron-rich foods and reduce blood loss from intolerance to cow's milk proteins.
  - Soy-based formulas can lead to blood loss, so children with milk enteropathy should be switched to a primary diet of iron-containing solids, an extensively hydrolyzed formula, or an amino acid–based formula.
- In the absence of ongoing blood losses, response to iron therapy is rapid and predictable.
  - Response with decreased irritability and increased appetite has been noted within 12–24 hours.
  - Reticulocyte response peaks 5–7 days after the institution of iron therapy.
  - In an otherwise healthy individual, recovery from anemia is approximately two-thirds complete within 1 month.
  - Anemia, microcytosis, and increased free RBC protoporphyrin levels are corrected completely with 3–5 months of treatment.
- Follow-up.
  - Hb should be measured again at 1 month to check progress and emphasize compliance.
  - If, after 4 weeks, anemia does not respond despite compliance and absence of acute illness, consider further evaluation by other laboratory tests, including MCV, RDW, and serum ferritin concentration.

Intravenous (IV) Iron

- IV infusions do not appear to be associated with severe adverse events or increased risk for infections as was previously suspected.
- With the exception of high-molecular-weight dextran preparations, iron infusions have been found safe and only associated with infusional reactions, which may be related to premedication.
- The availability of new IV iron formulations with improved safety profile and ease of administration has expanded the use of this option in select populations.
- Iron sucrose and ferric gluconate can be used to administer a total dose of iron in 1-hour infusions.
- Newer iron products (eg, ferumoxytol).
  - More avidly bind iron, minimizing release of labile iron during infusion.
  - Permit large-dose infusions that can be routinely administered in as little as 15 minutes with an acceptable safety profile.
- Typically reserved for a select group of patients.
  - Chronic kidney disease
  - Failure of iron absorption because of inflammatory bowel disease or bariatric or other gastrointestinal surgery
- Ease of administration is expanding consideration of their use in other populations.

Blood Transfusion

- Indicated only when severe anemia leads to congestive heart failure and cardiovascular compromise.
- If a blood transfusion is clinically warranted, packed RBCs should be given slowly or a partial exchange transfusion performed.
- Vital signs should be monitored carefully.

Failure to Respond

- When a patient fails to respond to oral iron treatment, the following factors should be considered:
  - Noncompliance with oral therapy
  - Inadequate iron dose
  - Persistent or unrecognized blood loss
  - Malabsorption of iron (eg, primary GI disease)
  - Other diagnoses (eg, α- or β-thalassemia trait, HbE disease)
  - Poor iron utilization (eg, chronic inflammatory disease, sideroblastic anemia, lead poisoning, congenital atransferrinemia)

WHEN TO ADMIT

- The patient exhibits signs of cardiac failure.
- The patient requires IV iron.
- The patient has moderate to severe blood loss.

WHEN TO REFER

- The cause of anemia is unknown.
- GI blood loss is suspected.
- Anemia is not explained by nutritional imbalance.
- Anemia is refractory to treatment.
- The patient requires IV iron.
- The diagnosis of iron deficiency is questionable.

FOLLOW-UP

- After iron therapy is initiated, the patient should be reevaluated at 1 month.
  - If, despite compliance, there is no response to treatment, an alternate diagnosis should be considered.

COMPLICATIONS

- Iron is an important ingredient of Hb and is involved in numerous cellular processes.
- Children with iron deficiency in infancy have
  - Poor cognition
  - Poor school achievement
  - Increased behavior problems into middle childhood
- Iron deficiency is also associated with deficits in work productivity.
- Severe anemia is associated with maternal and child mortality.

PROGNOSIS

- Prognosis for nutritional iron deficiency is good.

PREVENTION

- Prevention is an important public health issue.
- Iron balance is maintained by regulation of iron absorption.
  - Depends on amount and bioavailability of dietary iron and on regulation of iron absorption by the intestinal mucosa.
  - Most dietary iron occurs in the nonheme form and is much less bioavailable than that in heme proteins.
  - The iron in Hb and myoglobin is particularly bioavailable; ≤30% is directly absorbed by the GI tract.
  - Human milk and cow's milk contain small amounts of iron (0.2–0.3 mg/1,000 mL).
    - 50% of the iron in human milk is absorbed, compared with only 10% in cow's milk.
    - Full-term infants who are exclusively breastfed for the first 6–9 months do not become iron deficient.
  - Nonheme iron absorption is inhibited by
    - Bran in cereals
    - Polyphenols in many vegetables
    - Tannins in tea
  - Complementary foods, including fortified cereals, vegetables with high iron content, and red meats, should be introduced early.
- Increased iron intake among infants has resulted in a decline in childhood IDA in the United States.
- Use of screening tests has become a less efficient means of detecting iron deficiency in some populations, whereas for women of childbearing age, iron deficiency has remained prevalent.
- The Centers for Disease Control and Prevention (CDC) has developed recommendations for primary prevention of iron deficiency through appropriate dietary intake and secondary prevention through detecting and treating IDA.

CDC Recommendations

Prevention in Infants, Young Children, and Adolescents[1]

- Breastfeeding and iron-fortified formula
  - Full-term, healthy infants are at increased risk for iron deficiency after 4 months.
    - Exclusively breastfed or partially breastfed infants should be started on an oral iron preparation at 1 mg/kg/d at age 4 months to be continued until the introduction of iron-containing complementary foods, red meats, or vegetables with high iron content.
  - The iron needs of formula-fed infants can be met by standard formula and complementary foods, including iron-fortified cereal introduced >4–6 months.
  - Whole milk should not be introduced before age 12 months.
  - Infants 6–12 months of age should receive 11 mg iron/d.
  - Complementary foods, red meats, and iron-rich vegetables should be introduced early.
    - If iron requirements are not met, an oral iron preparation at 1 mg/kg/d should be given.
  - Toddlers 1–3 years of age should receive a daily iron intake of 7 mg through iron-fortified cereals, red meats, and iron-rich vegetables.
    - If iron requirements are not being met, they should receive an oral iron preparation at 1 mg/kg/d.
  - Children >3 years may receive chewable multivitamins.
  - Preterm infants require 2 mg/kg/d of iron starting at age 1 month through weaning to an iron-fortified formula or complementary food that can provide daily iron requirement of 2 mg/kg/d.
- Solid foods
  - At age 4–6 months or when the extrusion reflex disappears, recommend that infants be introduced to plain, iron-fortified infant cereal.
  - ≥2 servings per day of iron-fortified infant cereal can meet iron requirement at this age.
  - By ~6 months of age, encourage one feeding per day of foods rich in vitamin C (eg, fruits, vegetables, juice) to improve iron absorption, preferably with meals.
  - Suggest introducing plain, pureed meats >6 months or when the infant is developmentally ready.
- Adolescent girls and nonpregnant women
  - Encourage adolescent girls and women to eat iron-rich foods and foods that enhance iron absorption and to optimize their dietary iron intake.

Screening for Iron Deficiency in Infants, Children, and Adolescents[1]

- Universal screening for iron deficiency should occur at age 12 months and 6 months later and should include evaluation of Hb and risk factors for iron deficiency, such as
  - Preterm or low birth weight infants
  - Infants fed a diet of non–iron-fortified infant formula for >2 months
  - Infants introduced to milk <12 months
  - Breastfed infants who do not consume a diet adequate in iron >6 months (ie, who receive insufficient iron from supplementary foods)
  - Children who consume >24 oz per day of cow's milk
  - Children who have special health care needs
    - Children who use medications that interfere with iron absorption
    - Children who have chronic infection, inflammatory disorders, restricted diets, or extensive blood loss from a wound, an accident, or surgery
- If, at 12 months of age, Hb is <11 g/dL, additional evaluation for IDA should be undertaken.
  - Ferritin
  - Transferrin saturation
  - sTfR with CRP
  - CHr
- In mild anemia (Hb 10–11 g/dL), an alternative diagnostic approach would be to document an increase of Hb by at least 1 g/dL following 1 month of appropriate therapeutic doses of an oral iron preparation.
- Annual assessment of children aged 2–5 years for risk factors for IDA.
  - Low-iron diet
  - Limited access to food because of poverty or neglect
  - Special health care needs
- In populations of infants and preschool-aged children at high risk for IDA, screen all children for anemia between ages 9 and 12 months, 6 months later, and annually from ages 2–5 years.
  - Children from low-income families

- Children eligible for the Special Supplemental Nutrition Program for Women, Infants, and Children
- Migrant children
- Recently arrived refugee children

- Starting in adolescence, screen all nonpregnant women for anemia every 5–10 years throughout childbearing years during routine health examinations.
- Annually screen for anemia women having risk factors for iron deficiency.
  - Extensive menstrual or other blood loss
  - Low iron intake
  - Previous diagnosis of IDA

REFERENCE

1. From Centers for Disease Control and Prevention. Recommendations to prevent and control iron deficiency in the United States. *MMWR Recomm Rep.* 1998;47(RR-3):1–29; and Baker RD, Greer FR; American Academy of Pediatrics Committee on Nutrition. Diagnosis and prevention of iron deficiency and iron-deficiency anemia in infants and young children (0–3 years of age). *Pediatrics.* 2010;126(5):1040–1050

Irritability

DEFINITION

- Irritability is excessive response to a stimulus.
- Not a quantifiable symptom.
  - Includes episodes of crying or fussiness despite attempts to comfort

HISTORY

- Acute irritability may be associated with life-threatening illnesses requiring urgent intervention and stabilization before a search for the cause can begin.
- A parent who seeks care for an infant who is fussier than usual may arrive with an infant who is in shock or respiratory distress or who is having a seizure.
- If the child's condition is not immediately life-threatening, a complete history and thorough physical examination are the first steps in evaluation and, in many cases, will reveal the cause of the symptom.

PHYSICAL EXAMINATION

- A thorough head-to-toe examination, including special attention to the eyes, ears, digits, and genitalia, is essential to establish a diagnosis.
- Irritability and nonspecific crying episodes may be related to
  - Foreign body in the ear or nose
  - Corneal abrasion
  - Hair wrapped around a digit or penis
  - Diaper rash
  - Nonspecific vaginitis
  - Balanitis
  - Insect and spider bites or stings
  - Vaccination pain
- A systematic search for injuries should be performed on any child with a history of trauma.
  - Inflicted injuries are more difficult to diagnose.
  - Signs may be subtle, and the history often is misleading.
  - Causes may be easily apparent, such as fractures or dislocations.

DIFFERENTIAL DIAGNOSIS

Acute Irritability in the Ill-Appearing Child

Central Nervous System

- Children <2 years are at high risk for significant brain injury after accidental and non-accidental traumatic head injury.
  - Overall rates of brain injury are
    - ~13% in the 0- to 2-month age group
    - 6% in the 3- to 11-month age group
    - 2% in children >12 months
  - A history of a fall is often found.
  - A high index of suspicion should be maintained in infants <3 months.
- Concussion may be sustained from sports-related injuries.
  - The term *post-concussive syndrome* refers to a constellation of acute symptoms, which can be
    - Somatic (headache, dizziness, blurriness)
    - Emotional (irritability, anxiety)
    - Cognitive (concentration and memory difficulties)
  - The term *second impact syndrome* has been proposed for an athlete who
    - Has sustained a concussion and then sustains a second head injury before symptoms associated with the first have fully cleared.
    - These athletes are at risk for a catastrophic outcome, such as permanent disability or death.
- Brain tumor.
  - Increased intracranial pressure (ICP) from a brain tumor may produce acute irritability and altered behavior without the usual preceding symptoms (eg, headache or loss of coordination and ataxia).
  - Diagnosis may be delayed in young children because their symptoms are subtle (eg, headache, irritability, drowsiness) or similar to those of more common illnesses, such as gastrointestinal disorders (eg, vomiting).
- Hydrocephalus.
  - Causes increased ICP.
  - Often occurs in infancy with irritability, vomiting, a tense or bulging fontanel, and an increasing head circumference that crosses percentile lines.
  - Older children usually complain of headaches.

- Neuroimaging shows congenital malformation (eg, myelomeningocele, Budd-Chiari syndrome, Dandy-Walker malformation, aqueductal stenosis, arteriovenous malformation) or germinal matrix intraventricular hemorrhage of prematurity.
- Obstruction, infection, or malfunction of the ventriculoperitoneal shunt may lead to over- or under-drainage, initially causing irritability, headache, vomiting, or lethargy.

- Undiagnosed migraine headache may be the reason for irritability in the preverbal child.
  - Migraine headaches occur in 8%–12% of children <3 years.
- Seizures.
  - Children with seizures, especially unwitnessed, may appear irritable during an aura or the postictal phase.
  - Neonatal seizures.
    - More common in preterm newborns than term newborns
    - May have only subtle symptoms
      - Ocular or pedaling movements
      - Lip smacking
      - Apnea
  - Nonconvulsive status epilepticus, which includes absence and partial complex seizures, is a relatively rare cause of abnormal behavior.
    - Produces continuous or intermittent seizure activity in the absence of any motor component and without a return to baseline for >30 minutes.
    - Irritability and a change in behavior or mental status may be associated findings.
- Infant botulism.
  - Initial findings may include
    - Difficulty in feeding
    - Irritability
    - Lethargy
    - Weak cry
    - Constipation
  - Findings in advanced disease may include
    - Drooling
    - Dysphagia
    - Loss of head control
    - Respiratory distress and flaccid paralysis from progressive bulbar involvement

Infections

- Bacterial infection should be suspected in a child with fever and irritability.
- Meningitis.
  - Infants with meningitis may have irritability, lethargy, and poor feeding.
  - If the fontanel is still open, it may be bulging.
  - Group B streptococci and gram-negative bacilli are the most common causes in infants <3 months.
  - Beyond 3 months, *Streptococcus pneumoniae* and *Neisseria meningitidis* are the most common pathogens.
- Encephalitis from herpes simplex virus should also be considered in infants <3 months.
- Irritability and decreased movement of a limb should raise concern for osteomyelitis.
  - Swelling and erythema of the soft tissue overlying the bone may exist, often with a history of preceding trauma.
- Joint pain, fever, irritability, and a limp should raise concern for septic arthritis.
  - Examination reveals erythema, swelling, or warmth over the affected joint, with restricted movement.
  - With septic arthritis of the hip, swelling and redness may not be visible, and the pain may be referred to the knee.
  - An orthopedist should be consulted for possible surgical drainage.
- Children with Kawasaki disease, a vasculitis likely triggered by an unknown infectious agent, are often more irritable than patients with other febrile illnesses.
  - The principle clinical manifestations of this systemic vasculitis are fever, rash, conjunctival injection, erythema of lips and mouth, cervical adenopathy, and changes in the extremities.
- Bacteremia and urinary tract infections can produce irritability, along with fever, in an ill-appearing infant.

Trauma

- Abusive head trauma (shaken baby syndrome)
  - Occurs most commonly in children <2 years.
  - The rotational forces sustained during shaking cause movement of the brain within the subdural space and tearing of the bridging veins.
  - Clinical signs may be poor feeding, vomiting, lethargy, or irritability.

- Blunt trauma
  - In infants and young children, pressure from the lap belt of a restraint system in a motor vehicle crash or other blunt abdominal trauma can lead to intra-abdominal bleeding, initially displayed as irritability from tissue hypoperfusion and pain.
- Occult fracture

Acute Abdomen

- Intussusception is most common between the ages of 3 months and 5 years, with a peak incidence at 6–11 months.
  - The infant appears colicky, cries, and may draw the knees upward toward the chest; this may last a few minutes and then subside.
  - The infant often looks better between episodes, and irritability gradually increases and vomiting becomes more frequent and sometimes bilious.
  - The classic triad is intermittent colicky abdominal pain, vomiting, and bloody stools.
    - This triad is present in >65% of cases.
- Malrotation with midgut volvulus peaks during the first month of life but can occur anytime in childhood.
  - The neonate will be irritable initially.
  - As bowel becomes obstructed and necrotic, bilious vomiting and shock may result from perforation.
- Appendicitis is the cause of abdominal pain in 2%–3% of children seen in ambulatory clinics or emergency departments.
  - Abdominal pain in a young child may first manifest as irritability, before the appearance of nausea, vomiting, fever, and right lower quadrant tenderness.
  - Perforation rates for appendicitis are higher in children (30%–60%) than in adults.
  - Because the omentum is less developed in children, perforations are less likely to be walled off or localized.
- Hypertrophic pyloric stenosis may become symptomatic as early as the first week of life and as late as the fifth month.
  - Symptoms begin with non-bilious vomiting after feeding.
  - As the disease progresses, vomiting becomes projectile.
  - The infant may appear normal initially, but hunger makes the infant irritable, and signs of dehydration eventually become apparent.
  - An olive-shaped mass in the right upper quadrant of the abdomen is diagnostic and confirmed by ultrasound.
- Necrotizing enterocolitis typically is seen in preterm newborns in their first few weeks of life.
  - It may be seen rarely in full-term newborns, within the first 2 weeks after birth, particularly with a stressor, such as infection or anoxic event.
  - Newborns are ill appearing, irritable, and lethargic, with distended abdomen and bloody stools.
- Inguinal hernia.
  - 60% of incarcerated inguinal hernias occur during the first year of life, especially in infants born preterm, with symptoms of irritability, vomiting, and pain in the groin and abdomen.
  - On examination, a non-fluctuant tender mass is present in the inguinal region and may extend down into the scrotum.
  - With the onset of ischemia of the involved bowel, pain becomes more intense and localized to the scrotum, and the infant may have bilious vomiting with the presence of bloody stools.
- Irritability with scrotal pain also may result from epididymitis, torsion of the testis, or torsion of the appendix testis.
  - Testicular examination is imperative in all boys with irritability or abdominal pain.

Cardiac System

- Acute myocarditis
  - 3 phases have been identified in the pathogenesis.
    - Viral replication
    - Autoimmune injury to myocytes
    - Dilated cardiomyopathy
- Anomalous left coronary artery originating from the pulmonary artery
  - Occurs in early infancy with irritability during or soon after feedings.
  - Associated signs may include poor weight gain, diaphoresis, a murmur, and respiratory distress.
- Supraventricular tachycardia
  - May cause irritability and poor feeding

Hypoxic or Ischemic Events

- Carbon monoxide (CO) poisoning and methemoglobinemia cause irritability in response to hypoxia.
  - A history of smoke inhalation and exposure to an indoor gas stove or automobile exhaust fumes is indicative of CO poisoning.
    - Early findings are influenza-like: headache, irritability, and dizziness.
    - Prolonged exposure may result in altered mental status.

- Methemoglobinemia is characterized by
  - Blue-gray cyanosis that does not improve with oxygen
  - Normal arterial oxygen tension
  - Chocolate brown appearance of arterial blood
- In infancy, methemoglobinemia may be hereditary, a form that is usually mild.
- Acquired methemoglobinemia may be related to
  - Hypoxic events
  - Medication use (sulfonamides, topical anesthetics, metoclopramide)
  - Ingestion of products containing nitrites and nitrates (eg, contaminated well water; foods with naturally occurring nitrates, such as spinach, green beans, carrots, and squash)
  - Diarrhea, probably from nitrite-forming bacteria in the gut
- Pulse oximetry will not be reliable, as high levels of methemoglobin will tend to cause a pulse oximeter reading of ~85% regardless of the true level of oxygen saturation.

- Sickle cell anemia.
  - Ischemia may cause a painful vasoocclusive crisis.
  - Initial presentation in infants and younger children usually is irritability and dactylitis (painful swelling of the hands and feet as a result of vascular stasis and ischemia).

Metabolic System

- Hypoglycemia, hyponatremia or hypernatremia, hypocalcemia or hypercalcemia, hypomagnesemia, and inborn errors of metabolism can all cause irritability.
- Hypoglycemia is defined as a glucose level ≤40 mg/dL.
  - Can be a primary process
  - Can be caused by sepsis, ingestion, or cardiac or respiratory failure
- Hyponatremia can result from gastrointestinal losses or water intoxication.
- Hypernatremia is seen with diarrhea in which the water losses exceed salt loss, when replacement fluid has too high a sodium content, or with improper preparation of infant formula.
- Hypocalcemia.
  - In the newborn period, it may cause irritability, poor feeding, and lethargy.
  - Later in infancy and during childhood, it is seen with rickets.
  - Hypomagnesemia is found with hypocalcemia.
- Hypercalcemia is a rare electrolyte disturbance resulting from hyperparathyroidism, vitamin D intoxication, or idiopathic causes.
- Inborn errors of metabolism that cause irritability are those in which a toxic intermediate accumulates.
  - Organic and aminoacidemia and urea cycle disorders result in metabolic acidosis or hyperammonemia.
    - Symptomatic in the first few weeks of life, with vomiting, poor feeding, irritability, and lethargy
  - When a milder degree of enzyme dysfunction is present, clinical disease may be triggered by a bacterial or viral illness.

Toxins and Drugs

- Life-threatening intoxications may result from
  - Heavy metals, such as lead and mercury
  - Drugs of abuse, such as cocaine and alcohol
  - Envenomations by scorpions and snakes
  - Overdoses of or idiosyncratic reactions to medications
  - Contact with agricultural, industrial, or household chemicals
- Thorough questioning about recent use of lawn chemicals, pesticides, and cleaning products may be the only clues to these factors as a cause of irritability, because many are not detected by standard toxicologic screening.
- Prescribed or over-the-counter medications may cause irritability, even when used as directed and certainly when overused.
  - β-Agonists
  - Antiepileptics
  - Decongestants
  - Antihistamines
  - Antitussives
  - Various cold medicines
- Certain drugs of abuse are known to cause irritability.
  - Cocaine
  - Alcohol
  - Phencyclidine hydrochloride
  - Inhalants
- Exposure in infants and children may occur
  - By passive means
    - Transplacentally
    - Ingestion of human milk
    - Inhalation
  - By accidental ingestion

- A positive history may be difficult to elicit, and toxicologic screen may not always be helpful; thus, a strong index of suspicion is needed.
- Substance use or withdrawal should be considered in the differential diagnosis when any adolescent has chronic persistent irritability.
- In rare instances, intentional poisoning may be the cause of a child's distress.

Malignancy

- Cancers of all sorts may have irritability among their symptoms and must be considered carefully when no other diagnosis is forthcoming.
- Irritability and intermittent fever sometimes indicate leukemia with bone pain.

Acute Irritability in the Well-Appearing Child

- Irritability in infants has been attributed to a variety of causes of pain or discomfort that may become obvious during the evaluation.
- Dental caries and teething may cause an infant to be fussy or irritable.
  - Teething may be accompanied by loose stools but not fever.
  - Cold teething rings may provide some relief, but numbing gels with benzocaine are less helpful and may be associated with methemoglobinemia.
- Acute otitis media is a common cause of irritability, with or without fever, in children <2 years and in those attending child care.
- Gastroesophageal reflux.
  - Particularly common in the first year of life
  - May be asymptomatic
  - May be indicated by postprandial irritability, recurrent vomiting, and inadequate weight gain
- Other sources of irritability and nonspecific crying episodes may be related to
  - A foreign body in the ear or nose.
    - If present for a prolonged period, results in foul-smelling discharge.
    - Disk batteries need to be removed emergently because they may leak and can cause tissue destruction.
    - An insect in the ear canal can make a child very irritable and may be removed after first killing the insect with mineral oil or lidocaine.
  - Corneal abrasion.
    - May be caused by foreign bodies under the eyelid, inward-turned eyelashes, or eye scratching
    - Irritability, increased tearing, conjunctival injection, and photophobia
    - Foreign body may be removed by a moistened cotton-tipped applicator or irrigation.
  - A hair tourniquet around the digit or genitals can cause pain and irritability.
    - Thorough examination of creases is essential; prolonged constricting bands may compromise distal circulation.
  - Thorough examination of the genitalia may reveal evidence of vaginitis, balanitis, or anal fissure.
  - Diaper dermatitis, common after a diarrheal illness, with *Candida* infection, or as an allergic reaction to the diaper material.
  - Insect and spider bites or stings.
- Infants may be irritable after vaccination, with local erythema, swelling, and tenderness at the injection site.
  - Persistent, inconsolable crying lasting ≥3 hours within 48 hours of receiving diphtheria, tetanus, whole-cell pertussis vaccine has been reported but not with the newer diphtheria, tetanus, acellular pertussis vaccine.

Chronic Irritability

- Chronic irritability may be recurrent or persistent.
  - Psychosocial causes are most common.
  - Toxic, neurologic, metabolic, and miscellaneous causes.
  - Abuse and neglect.
- Irritability as a chronic feature of a child's behavior may indicate significant problems with familial relationships and the ability to master the environment.
  - Infants may be irritable because of maternal-infant temperament mismatches, maternal depression, or stress within the family.
- An older child or adolescent who has a psychiatric problem, such as depression, psychosis, autism spectrum disorder (ASD), posttraumatic stress disorder, or substance abuse, may be described as "irritable."

Chronic Recurrent Irritability

- Colic
  - Usually occurs in infants <5 months
  - Characterized by paroxysms of screaming, which may persist for several hours
  - Criteria for diagnosis
    - Crying for ≥3 hours per day
    - For ≥3 days per week
    - For ≥1 week
  - Typically peaks at 6 weeks and abates by 3–4 months
- Constipation
  - Associated with inadequate fluid intake, low-fiber diet, dietary changes, and toilet training.
  - Large, hard stools can result in anal fissures that may make the child become increasingly reluctant to use the bathroom because of the pain.
- Food allergy
  - Affects ~6%–8% of infants and young children and ~3.5%–4% of adults
  - The most common food allergens include cow's milk, eggs, peanuts, wheat, and shellfish.
  - Milk protein allergy usually is seen in the first few months of life.
    - Irritability and blood-streaked stools, although otherwise healthy.
    - Treatment involves switching to hypoallergenic formulas derived from cow's milk, and then gradually advancing to an unrestricted diet by 9–12 months of age.
- Sleep disturbance
  - Night terrors
    - Typically occur between 2 and 4 years of age during nonrapid eye movement sleep
    - Usually begin with sudden and prolonged periods of inconsolable crying and end spontaneously, with the child rapidly returning to sleep
  - Nightmares
    - A nightmare occurs during rapid eye movement sleep, characterized by a frightening dream that fully wakes the child; return to sleep is delayed.
    - Vivid recollection of dream appropriate to the child's developmental and maturational stage.
- Neurologic disorders
  - Brain tumors
  - Migraine headaches
  - Seizures
  - Postconcussion syndrome
    - Particularly distressing to families because head injury may have occurred months or years before and may have seemed minor, yet irritability and behavior changes may be persistent.

Chronic Persistent Irritability

Psychosocial Disorders

- Attention-deficit/hyperactivity disorder is the most commonly diagnosed biological-behavioral disorder of childhood, occurring in ~8%–10% of school-aged children.
  - Children may have coexisting externalizing disorders (conduct disorder and oppositional defiant disorder) and internalizing disorders (depression and anxiety disorders).
  - A common presentation in infants and young children may be irritability from frustration as a result of family and peer relationships, propensity to accidental injury, and difficulty with academic work.
- ASD usually occurs in children <3 years.
  - Early symptoms include irritability, deficits in verbal and social interaction, repetitive behaviors, failure to participate within groups, and hours spent in solitary play.

Children With Cognitive Impairments

- Children with severe intellectual disabilities cannot verbalize what they are experiencing and are left to endure pain more often than healthy children.
  - Although caregivers are usually adept at reading a child's body language and behaviors to know when the child is in pain, they often cannot identify the specific cause.
  - These children are likely to experience pain from the same sources as unimpaired children (eg, teething, sore throat, headache, minor trauma) but are at risk for additional sources of pain and discomfort.
  - Constipation, muscle spasms, and irritation from feeding tubes are frequent causes of irritability.
- Children with intellectual disabilities often receive multiple drugs for seizures, respiratory conditions, and constipation, with a high incidence of behavioral side effects (irritability, aggression, and hyperactivity).
- In children with spastic quadriplegia, pathologic fractures are a common finding, related to limb rigidity, joint contractures, bone demineralization, and anticonvulsants.

- A wide variety of chronic disorders have irritability as a prominent or sole component.
- Hormonal effects associated with adolescence in boys and girls can cause moodiness and irritability.

LABORATORY EVALUATION

- Infection
  - Cultures
  - Complete blood cell count
  - Erythrocyte sedimentation rate
  - C-reactive protein
- Metabolic system
  - Glucose
  - Sodium
- Toxins and drugs
  - Blood and urine screening
- Acute myocarditis
  - Serum troponin level
- CO poisoning
  - Arterial measurement of carboxyhemoglobin

IMAGING

- Unexplained irritability or lethargy, or a scalp hematoma in an irritable child, protracted vomiting, or neurologic deficits, all warrant computed tomography (CT) of the head.
- Plain films, ultrasonography, magnetic resonance imaging (MRI), and bone scanning can be helpful in the evaluation of
  - Suspected bone abnormalities
    - — Fractures
    - — Osteomyelitis
    - — Infarction in sickle cell disease
  - Joint processes
    - — Septic arthritis, particularly of the hip
    - — Trauma
- Plain films of the abdomen can be helpful in diagnosing
  - Necrotizing enterocolitis (pneumatosis intestinalis)
  - Malrotation with midgut volvulus
- Ultrasonography and CT can be helpful with intra-abdominal processes.
  - Appendicitis
  - Intussusception
  - Pyloric stenosis
  - Blunt abdominal trauma
- Acute myocarditis.
  - Echocardiogram will show reduced ventricular function.
  - Chest radiograph may reveal cardiomegaly, pulmonary edema, or pleural effusion.
  - Cardiac MRI can confirm the diagnosis.
- Anomalous left coronary artery originating from pulmonary artery.
  - Cardiomegaly on radiograph is almost universal.

DIAGNOSTIC PROCEDURES

- Corneal abrasion.
  - Diagnosis is made by Wood lamp examination after instillation of fluorescein into the eye.
- Acute myocarditis should be considered in an irritable child with tachycardia, especially if accompanied by poor perfusion.
  - An electrocardiogram (ECG) may reveal sinus tachycardia, ventricular hypertrophy, and ST and T wave changes. Low-voltage QRS complexes, or an abnormal QRS axis, may be present.
  - Endomyocardial biopsy can confirm diagnosis.
- Anomalous left coronary artery originating from pulmonary artery.
  - Myocardial ischemia on ECG is almost universal.
  - The ECG may reveal abnormal Q waves in leads V4–V6, I and aVL, or an abnormal R wave progression.
- Nonconvulsive status epilepticus.
  - Electroencephalography can be diagnostic.

TREATMENT APPROACH

- Treatment is based on the cause of irritability.

SPECIFIC TREATMENT

- Infections should be treated with intravenous antibiotics.

WHEN TO ADMIT

- Neonates <1 month who are irritable, for evaluation and observation
- Children in whom child abuse and neglect are suspected
- Children with a life-threatening condition, such as meningitis or brain tumor, that causes irritability

Jaundice

DEFINITION

- *Jaundice* is a yellowish discoloration of skin, sclerae, and mucous membranes that results from deposition of the bile pigment bilirubin.
- Jaundice becomes evident at the following serum bilirubin concentrations:
  - >3 mg/dL in older children
  - >5 mg/dL in newborns
- *Hyperbilirubinemia* is defined as total serum bilirubin concentration >1.5 mg/dL.
  - Typically characterized by the fraction of bilirubin that is increased, unconjugated (indirect), or conjugated (direct).
  - *Conjugated hyperbilirubinemia* refers to direct bilirubin concentration >2 mg/dL or >20% of the total bilirubin concentration.
  - The presence of conjugated hyperbilirubinemia suggests hepatobiliary tract conditions.
- *Neonatal cholestasis* refers to infants <3 months who have cholestatic jaundice regardless of the cause.
  - Number of patients with identified cause has increased with availability of new diagnostic techniques.

HISTORY

- A detailed history is essential when evaluating a patient with jaundice.
- Special attention should be paid to the presence of
  - Viral prodrome
  - Abdominal pain or distention
  - Acholic stools
  - Dark urine
  - Pruritus
- In patients with neonatal jaundice, focus on
  - Prenatal history
  - Birth history
- In older children, focus on
  - Patient's age at onset of jaundice
  - Exposure to hepatotoxic agents
- Detailed family history should include
  - Information about the presence of persistent jaundice
  - Chronic liver diseases
  - Hemolysis
  - Metabolic diseases
- Goals of initial evaluation are to distinguish
  - Acute from chronic liver diseases
  - Intrahepatic processes from extrahepatic biliary tract obstruction
  - Primary liver diseases from systemic diseases

PHYSICAL EXAMINATION

- Patients with jaundice from unconjugated hyperbilirubinemia have bright yellow skin.
- Patients with jaundice from conjugated hyperbilirubinemia have dark green-yellow skin.
- Patients should undergo a complete physical examination, with special focus on
  - General appearance
  - Growth and development
  - Signs of cardiovascular dysfunction
  - Neurologic signs
  - Organomegaly
- The size and character of the liver should be determined.
  - The newborn or infant liver is a large organ relative to body size.
    - In newborns, mean liver span is 5.9 cm along the midclavicular line, calculated by measuring the distance between the percussed upper and palpated lower liver edge.
    - Normal infant liver may be palpable and is typically <2 cm below the right costal margin.
  - Consistency and character of the liver edge may help determine the nature of underlying liver disease.
    - Enlarged liver resulting from an acute intrahepatic process is usually tender but soft.
    - Cirrhotic liver may have a hard and irregular edge, but its edge is not always palpable.
- Thorough abdominal examination to identify
  - Enlarged spleen
    - In newborns and infants, the tip of the spleen can normally be palpated below the left costal margin.
    - Splenomegaly in a patient with underlying liver disease implies portal hypertension, especially in the presence of ascites and a prominent abdominal cutaneous venous pattern.
  - Other abdominal masses
  - Areas of tenderness
  - Ascites
  - Abdominal cutaneous venous pattern
  - Other physical findings may indicate a particular cause, such as
    - Xanthomas in primary biliary cirrhosis
    - Kayser-Fleischer rings in Wilson disease
    - Characteristic facial features and posterior embryotoxon in Alagille syndrome

DIFFERENTIAL DIAGNOSIS

General

- Differential diagnosis of jaundice is categorized as unconjugated or conjugated and in 2 age groups.
  - Newborns and young infants
  - Older infants and children
- Unconjugated hyperbilirubinemia is common in neonates but relatively rare thereafter.
  - Usually transient and benign, but marked increases of bilirubin can be toxic to the central nervous system (CNS).
- Conjugated hyperbilirubinemia is always pathologic.
  - When present in young infants, it is often related to
    - Primary hepatobiliary disorders
    - Systemic or metabolic diseases
    - Genetic defects in bilirubin and bile acid metabolism or transport
  - More prevalent in older children
    - Viral hepatitis
    - Drug- or toxin-induced liver damage

Jaundice in Newborns and Young Infants

Unconjugated Hyperbilirubinemia

- Non-physiologic jaundice should always be considered in neonatal jaundice.
- A pathological cause suggested by
  - Early onset
  - Rapid progression
  - Persistence >2 weeks after birth
- In most instances, pathological unconjugated hyperbilirubinemia results from excessive production of bilirubin or abnormal hepatic clearance of bilirubin.

INCREASED PRODUCTION OF BILIRUBIN

- Hemolysis (ABO or Rh incompatibility, erythrocyte defects, erythrocyte enzyme defects, disseminated intravascular coagulopathy [DIC])
  - The most common cause of excessive bilirubin production in neonates.
  - Usually observed within the first 24 hours of life.
  - Often seen in association with maternal-fetal blood type incompatibility (ABO or Rh incompatibility).
  - ABO incompatibility is usually seen in newborns with blood type A or B born to blood type O mothers.
    - Weakly positive direct Coombs (antiglobulin) test, high reticulocyte count, spherocytes on blood smear, and high levels of unconjugated bilirubin
  - Hemolytic disease in Rh incompatibility usually develops when an Rh-negative mother has become sensitized after exposure to Rh-positive fetal blood during a previous pregnancy.
    - Rh incompatibility is less common and usually more severe than ABO incompatibility.
    - Affected neonates usually develop jaundice in the first hours of life and have hepatosplenomegaly with a strongly positive direct Coombs test and anemia.
    - In severe cases, fetal hydrops from intrauterine hemolysis may be present at birth.
- Hemoglobinopathies
  - Polycythemia
    - Can cause an increase in bilirubin production as a result of absolute increase in erythrocyte mass
  - α-Thalassemia
    - Suspect in newborns with jaundice and moderate hypochromic, microcytic, hemolytic anemia
  - Erythrocyte enzyme defects
    - Glucose-6-phosphate dehydrogenase (G6PD) or pyruvate kinase deficiency may cause hemolysis at any age.
- Cephalohematoma resorption
  - Increased bilirubin production caused by rapid breakdown of erythrocytes in the extravascular space

DECREASED HEPATOCELLULAR UPTAKE OR CONJUGATION

- Preterm birth
- Physiologic jaundice of the newborn
  - Associated with decreased bilirubin UDP-glucuronosyl transferase (BUGT) activity
- Congenital hypothyroidism
  - Presumably caused by delayed maturation of BUGT
- Human milk jaundice
  - Usually occurs in a thriving breastfed newborn during the second and third weeks of life
  - Associated with decreased BUGT activity
- Drug toxicity
  - Aspirin, cephalosporins, and sulfonamides can impair bilirubin transport by altering bilirubin-albumin binding.
  - Rifampin can inhibit hepatocellular uptake of bilirubin.
- Gilbert and Crigler-Najjar syndromes
  - Familial unconjugated hyperbilirubinemias caused by mutations in gene encoding for BUGT

- Crigler-Najjar syndrome
  - Results from absent (type 1) or decreased (type 2) BUGT activity.
  - Type 1 is an autosomal-recessive disease and exhibits in the first hours of life with severe nonhemolytic jaundice.
  - Type 2 is an autosomal-dominant disease with less severe jaundice and may improve with phenobarbital to promote bile flow.
- Gilbert syndrome
  - Inherited as an autosomal-dominant trait, although autosomal-recessive pattern has been described.
    - Insertional mutation of *UGT1A1* gene results in reduced expression of the gene.
  - Seen clinically during prolonged fasting or in association with viral illness.

Conjugated Hyperbilirubinemia

- Also known as *cholestatic jaundice*
- Always pathologic
- It can result from
  - Impaired bile formation by the hepatocyte
  - Obstruction to the flow of bile through the intrahepatic or extrahepatic biliary system
  - Conditions associated with conjugated hyperbilirubinemia in the newborn/infant include
    - Primary hepatobiliary disorders
    - Genetic or metabolic diseases
    - Systemic infections
    - Drug toxicity

LIVER DISEASES

- Acute liver damage (ischemia, hypoxia, acidosis)
  - Conditions such as cardiopulmonary arrest, shock, and severe metabolic acidosis may cause an acute ischemic insult to the liver and hepatocyte necrosis.
  - Affected patients have a marked and rapid increase in serum aminotransferase levels and conjugated hyperbilirubinemia within 24–48 hours after the insult.
  - In most, liver function will normalize once the initial insult is corrected.
  - Rarely, patients may develop acute liver failure.
- Infection
  - Sepsis
    - The most frequently associated bacterial organisms are *Escherichia coli,* group B *Streptococcus,* and *Listeria monocytogenes*
  - TORCH (**t**oxoplasmosis, **o**ther agents, **r**ubella, **c**ytomegalovirus, **h**erpes simplex)
    - Low birth weight, hepatosplenomegaly, cutaneous manifestations, and ophthalmologic and CNS involvement.
    - Anemia, thrombocytopenia, increased aminotransferase levels, and cholestasis.
    - Other infections, such as HIV and hepatitis B and C, have decreased with improved prenatal screening.
  - Urinary tract infections
- Viral or other hepatitis
- Parenteral nutrition–associated liver disease
  - Soybean-based lipid emulsions are a major factor.
  - Lipid emulsions based on fish oil can reverse or prevent cholestasis.
    - Similar results from limiting soy-based lipid emulsions to ≤1 g/kg/d
- Metabolic liver diseases
  - Galactosemia
    - Inborn error of galactose metabolism with autosomal-recessive inheritance.
    - Results in accumulation of toxic metabolites of galactose-1-phosphate and galactitol in the liver.
    - Clinical picture varies from mild liver disease to fulminant hepatic failure, usually with vomiting, diarrhea, and poor feeding.
    - Multi-organ involvement.
    - Associated with risk for *E coli* sepsis.
  - Neonatal hemochromatosis
    - Usually born preterm, with intrauterine growth restriction.
    - Acute liver failure at birth or soon thereafter, with cholestatic jaundice, hypoglycemia, hypoalbuminemia, and coagulopathy.
    - Marked by excessive iron deposition in extrahepatic sites.
    - Typical laboratory findings include increased ferritin and transferrin saturation and relatively low transferrin levels.
    - Liver aminotransferase levels can be slightly increased or even normal.
  - α_1-Antitrypsin deficiency
    - Relatively common genetic disorder
      - Homozygous PiZZ genotype in 1 in 2,000 to 1 in 6,000 live births.
      - Only 10% of patients develop liver disease.
        - ▶ Liver injury from retained mutant α_1 ATZZ in the endoplasmic reticulum of hepatocytes.

- ▶ Typically become jaundiced early in infancy, although liver disease can have onset later in life.
- Tyrosinemia type 1 (hepatorenal tyrosinemia)
  - — Deficiency of fumarylacetoacetate hydrolase, an enzyme involved in tyrosine degradation, results in tissue accumulation of tyrosine and other intermediate metabolites.
  - — Varies from severe liver disease or acute liver failure in early infancy to chronic liver disease later in life.
  - — Also affects kidneys and peripheral nerves.
  - — Risk for hepatocellular carcinoma early in life.
  - — Markedly increased α-fetoprotein level.
  - — Presence of succinylacetone in urine or blood is pathognomonic.
  - — Early diagnosis is important because specific medical therapy can delay progression and improve quality of life.
- Primary mitochondrial hepatopathies
  - — Caused by a variety of defects, including mitochondrial DNA depletion, respiratory chain defects, fatty acid oxidation defects, and mitochondrial membrane enzyme defects.
  - — Symptoms usually develop with the first few months of life.
  - — Neuromuscular problems and marked lactic acidosis are common.

■ Hormones and drugs

OBSTRUCTION OF BILIARY SYSTEM

■ Congenital anomalies (biliary atresia, choledochal cyst)
- *Extrahepatic biliary atresia* (EHBA) is an idiopathic, destructive, inflammatory process of the extrahepatic and intrahepatic bile ducts.
  - — Neonates typically develop jaundice and acholic stools at ~2 weeks of age.
  - — In early stages, the stool may still have bile pigment.
  - — Diagnosis is confirmed with endoscopic retrograde cholangiopancreatography (ERCP) with cholangiogram or intraoperative cholangiogram.
    - ■ Portoenterostomy, Kasai operation, is performed in an effort to reestablish bile flow.

■ *Choledochal cysts* are rare congenital anomalies characterized by varying degrees of cystic dilation of the biliary tree.
  - — May be detected at any age; 18% of cases are diagnosed during the first year of life.
  - — Classic presentation of jaundice, abdominal pain, and right epigastric mass is rarely observed in infants and young children.
- *Alagille syndrome,* also known as *arteriohepatic dysplasia,* is inherited as an autosomal-dominant condition with variable penetrance.
  - — Characterized by paucity of intrahepatic bile ducts, peripheral pulmonary stenosis, butterfly vertebrae, posterior embryotoxon, and peculiar facies.
  - — Mutations in the *JAG1* gene are identified in most patients, and diagnosis is confirmed by genetic testing.
  - — Jaundice and pruritus are often the main clinical features during infancy.

DEFECTS OF BILIRUBIN METABOLISM OR TRANSPORT

■ Progressive familial intrahepatic cholestasis (PFIC)
- Identified as a distinct group of conditions involving intrahepatic cholestasis from bile acid transport defects leading to impairment of bile excretion.
  - — Affected patients often develop jaundice in the first few months of life.
  - — They may also have severe pruritus, growth failure, fat-soluble vitamin deficiency, abnormal coagulation profile, and increased serum bile acids.
  - — Disease usually progresses to cirrhosis and liver failure early in life.
- Three gene mutations account for the major subtypes of the condition (*PFIC1, PFIC2, PFIC3*), and genetic testing is available.

■ Dubin-Johnson syndrome, Rotor syndrome (See Bilirubin Metabolism or Transport Defects section.)

Jaundice in Older Infants and Children

■ In this age group, jaundice is an unusual sign and more often suggests a serious clinical condition.

Unconjugated Hyperbilirubinemia

■ Unconjugated hyperbilirubinemia is seen in older infants and children in association with
- Hemolysis
  - — Erythrocyte defects (eg, sickle cell anemia, hereditary spherocytosis)
  - — Erythrocyte enzyme defects (eg, G6PD deficiency)
  - — DIC
- Gilbert syndrome
  - — A benign disorder affecting ~7% of the population.

- Inherited as an autosomal-dominant trait, although an autosomal-recessive pattern has also been described.
- Jaundice does not typically develop until after puberty.
- Jaundice is usually intermittent and more evident with fasting or with the stress of an acute viral illness.
- Patients usually have mild unconjugated hyperbilirubinemia with otherwise normal liver function tests and no evidence of ongoing hemolysis.

Conjugated Hyperbilirubinemia

LIVER DISEASE

- Jaundice can result from acute or chronic viral hepatitis, autoimmune hepatitis (AIH), and drug- or toxin-induced injury.
- Viral hepatitis (hepatitis A, B, C, E).
  - Hepatitis A.
    - Children <5 years tend to be anicteric.
    - Rarely causes fulminant liver failure.
  - Hepatitis E has a clinical course similar to that of hepatitis A.
  - Hepatitis B or C infection is usually anicteric and chronic in children.
  - Other viruses (eg, Epstein-Barr virus, cytomegalovirus, adenovirus, enterovirus) can also cause acute hepatitis.
    - Jaundice is not always present.
- AIH is a progressive inflammatory condition of the liver of unknown etiology.
  - Usually progresses to cirrhosis if not promptly diagnosed and treated.
  - Should always be considered in a patient with jaundice associated with increased aminotransferase levels.
  - Jaundice is present in more than half of patients with AIH.
  - Hyperglobulinemia is often evident, and autoantibodies such as antinuclear antibody, anti-smooth muscle antibody, and anti-liver kidney microsomal antibody may be positive or negative.
  - When present, anti-liver kidney microsomal antibody categorizes the disease as AIH type 2.
    - May have a fulminant course and can present as acute liver failure
  - AIH type 1 is more common, with onset likely before adolescence.
- Toxins and drugs (ethanol, acetaminophen, isoniazid, phenytoin).
  - Initially suspected on the basis of circumstantial evidence.
  - Classified into 3 types, according to different clinical features.
    - Hepatitic
      - Acetaminophen overdose can cause acute hepatitis with zone 3 hepatocyte necrosis.
    - Cholestatic
      - Cholestasis is more prominent when damage to bile duct epithelial cells results in an impaired bile flow.
      - Can be caused by many different drugs, including estrogen or oral contraceptive pills, erythromycin, cyclosporine, and haloperidol.
    - Mixed hepatitic-cholestatic
  - Most cases of drug-induced liver damage spontaneously resolve once the drug responsible for the injury is withdrawn.
- Other liver diseases with conjugated hyperbilirubinemia include
  - Wilson disease.
    - An autosomal-recessive disorder of human copper metabolism.
    - Clinical onset usually >5 years of age.
    - Mutations in the *ATP7B* gene lead to impaired biliary excretion of copper, resulting in progressive accumulation of copper in the liver and subsequently in other organs and tissues.
    - Copper deposition in the liver can result in acute or chronic hepatitis, cirrhosis, or fulminant liver failure with severe cholestatic jaundice.
    - Hemolytic anemia, Kayser-Fleischer rings in the eyes, and neuropsychiatric symptoms are also manifestations of the disease.
  - Nonalcoholic fatty liver disease.
  - Acute liver damage: ischemia, hypoxia, acidosis.
  - Total parenteral nutrition related.
  - Pregnancy related (acute fatty liver of pregnancy, preeclampsia).
  - Infiltrative cancers may occur rarely and can cause jaundice at any age.

OBSTRUCTION OF THE BILIARY SYSTEM

- Choledochal cyst
- Cholelithiasis or choledocholithiasis
  - Most common cause of biliary obstruction in children.
  - Often found in patients with an underlying hemolytic disease.
  - Isolated gallstone disease can occur.
    - Older children usually present with vomiting and right upper abdominal pain, with or without jaundice.
- Cholecystitis
- Diseases of the bile ducts (primary sclerosing cholangitis, AIDS cholangiopathy)
  - Primary sclerosing cholangitis is characterized by stenosis, dilation, and fibrosis involving the intrahepatic or extrahepatic biliary tree, or both.
    - Most common form of chronic liver disease in children with inflammatory bowel disease.
    - Cholestatic jaundice is seen in <50% of affected patients.

BILIRUBIN METABOLISM OR TRANSPORT DEFECTS

- PFIC.
- Dubin-Johnson syndrome.
  - Recessively inherited disorder caused by mutations in the canalicular transporter gene, resulting in impaired secretion of conjugated bilirubin.
  - Chronic jaundice is the main clinical manifestation.
  - Characteristic brown to black discoloration of the liver resulting from pigment deposition in the lysosomes.
- Rotor syndrome.
  - Clinically similar to Dubin-Johnson syndrome but involving impairment of intracellular storage capacity of the liver for binding anions
  - Inherited as an autosomal-recessive disorder
- In Dubin-Johnson and Rotor syndromes, conjugated hyperbilirubinemia is present without abnormalities in other liver tests.

LABORATORY EVALUATION

- Serum bilirubin is conventionally measured by spectrophotometry based on the van den Bergh (diazo) reaction.
  - Conjugated (direct) bilirubin reacts rapidly with diazo reagents.
  - Unconjugated (indirect) bilirubin reacts slowly.
  - Indirect bilirubin is calculated as the difference between total bilirubin and direct bilirubin fraction.
  - Direct bilirubin consists of conjugated bilirubin and δ-bilirubin.
    - High-performance liquid chromatography can measure δ-bilirubin, as well as α-, β-, and γ-bilirubin.
- Initial laboratory studies in the evaluation of jaundice include
  - Complete blood cell count
    - Useful in detecting hemolysis, indicated by the presence of anemia with fragmented erythrocytes (schistocytes) and increased reticulocytes on the smear.
    - Thrombocytopenia is typically seen in patients with portal hypertension and hypersplenism.
  - Liver function tests
    - Isolated hyperbilirubinemia with otherwise normal liver function suggests hemolytic disease or bilirubin metabolism defects.
  - Coagulation profile
- Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels are the most frequently used markers of hepatocellular injury.
  - ALT is a more specific indicator of hepatocyte injury because AST also increases with hemolysis and myocardial or skeletal muscle injury.
  - In general, marked increase in AST and ALT occurs in severe viral hepatitis, acute toxin- or drug-induced hepatic necrosis, or ischemia.
  - Mild increase of AST and ALT is seen in nonalcoholic fatty liver disease, chronic viral hepatitis, and drug toxicity.
  - Declining AST and ALT levels usually indicate hepatocyte recovery.
    - In the course of fulminant liver failure, if seen in association with a worsening liver synthetic function, decreasing AST and ALT levels may be an ominous sign of massive hepatic necrosis, with few viable hepatocytes remaining to further release these enzymes.
  - AST and ALT are less useful in patients with chronic end-stage liver disease because they can be normal or only slightly increased in the presence of marked fibrosis of the liver.
- Alkaline phosphatase and γ-glutamyltransferase (GGT) are useful markers for intrahepatic and extrahepatic cholestasis.
  - In most hepatobiliary diseases, GGT and alkaline phosphatase are increased.
  - In PFIC (types 1 and 2), a normal or low GGT is observed in the presence of a high alkaline phosphatase.

- Isolated increase of alkaline phosphatase may be seen in patients with non-hepatobiliary diseases, such as bone disorders.
- Normal GGT values in newborns may be 5–8× greater than those in adults.

- Prothrombin time (PT) and albumin are used to evaluate hepatic synthetic function.
  - Abnormal PT results from impaired hepatic synthesis of coagulation factors I, II, V, VII, and X or deficiency of vitamin K (or both).
  - Parenteral administration of vitamin K generally normalizes a prolonged PT in patients with vitamin K deficiency associated with cholestatic jaundice but not in patients with hepatocellular disease.
  - In acute liver injury, markedly increased PT suggests the possibility of fulminant liver failure.
  - Hypoalbuminemia may be seen in patients with acute and chronic liver diseases.
  - In the early stages of acute liver injury, serum albumin may not be a reliable indicator of hepatic synthetic function because it has a long half-life (~21 days).
- Based on clinical information and results of initial tests, further evaluation, including imaging studies, may be warranted.
- Additional studies may include
  - Blood and urine cultures
  - Viral serologic studies
  - Toxin and drug screen
  - Autoimmune markers
  - α_1-Antitrypsin phenotype
  - Ceruloplasmin
  - Urine succinyl acetone
  - Serum bile acids
- In jaundiced newborns or young infants with abnormal liver function tests, TORCH titers should also be obtained.

IMAGING

- Ultrasonography
  - The most useful initial imaging modality in the assessment of the intrahepatic and extrahepatic biliary system in patients with jaundice.
  - Suggests such causes of jaundice as
    - Biliary atresia
    - Choledochal cyst
    - Hepatic cystic lesions
    - Cholelithiasis
  - When EHBA is a consideration
    - Ultrasound can exclude other causes of cholestasis, such as choledochal cysts, gallstones, or biliary sludge.
    - Absence of gallbladder or appearance of the triangular cord sign at the hilar region is suggestive of EHBA.
    - Presence of a gallbladder on sonography does not exclude EHBA.
- Computed tomography
  - May be preferred for assessing the general anatomy of the hepatobiliary system and possible non-cystic hepatic lesions
- Nuclear scintigraphy
  - Useful in diagnosis of acute cholecystitis or chronic acalculous cholecystitis
- Magnetic resonance imaging cholangiopancreatography (MRCP)
  - Noninvasive study that identifies abnormalities of the intrahepatic and extrahepatic biliary system.
- ERCP
  - Provides information similar to that of MRCP.
  - Allows possible therapeutic intervention.
    - Sphincterectomy
    - Biliary stone extraction
    - Stent placement
  - Diagnosis of EHBA is confirmed by ERCP with cholangiogram or intraoperative cholangiogram.

DIAGNOSTIC PROCEDURES

- Liver biopsy provides information on the histology and architecture of the liver.
  - Percutaneous liver biopsy is most commonly used in patients with persistently abnormal liver tests, especially when conventional laboratory and imaging studies do not lead to a firm diagnosis.
  - Use of liver biopsy to diagnose acute liver injury is limited because of commonly found nonspecific histologic changes.
  - Liver biopsy is usually performed in suspected EHBA, although histologic findings are not always conclusive.
- Punch biopsy of the lower lip mucosa for diagnosis of neonatal hemochromatosis.
  - The sample is analyzed for iron deposition in salivary glands.

SPECIFIC TREATMENT

Unconjugated (Indirect) Hyperbilirubinemia

- Treatment of newborns is based on the revised guidelines of the American Academy of Pediatrics.
  - Provide a framework for detecting neonatal hyperbilirubinemia and preventing kernicterus.
  - Emphasize the importance of
    - Systematic assessment of the risk of severe hyperbilirubinemia
    - Close follow-up
    - Prompt intervention when necessary

Conjugated (Direct) Hyperbilirubinemia

- Management should focus on correcting the underlying cause, optimizing nutrition, and controlling pruritus.
- Malabsorption of fat and fat-soluble vitamins is commonly seen in patients with cholestasis because they have impaired bile secretion.
- A diet high in medium-chain triglycerides should be used to promote growth in children with chronic cholestasis.
  - Medium-chain triglycerides are relatively water soluble and directly absorbed into the portal system, unlike long-chain triglycerides, which require bile acid micelles for solubilization.
- Supplementation of fat-soluble vitamins A, D, E, and K is essential.
  - Serum vitamin levels should be routinely followed to monitor adequate supplementation.

Cholestasis-Associated Pruritus

- Several different therapeutic agents have been used with very little success.
  - Ursodeoxycholic acid has been shown to lower serum bile acid.
  - Other agents have also been used.
    - Cholestyramine, a bile acid–binding resin
    - Rifampin

Liver Transplantation in Children

- Accepted therapy for many life-threatening liver diseases.
- Current survival rates for children after liver transplantation are
  - 90% at 1 year
  - 85% at 3 years
- Early referral and transfer to a liver transplant center are important to ensure a good outcome.
- EHBA is the most common indication for transplantation in children.
- Other indications include
  - α_1-Antitrypsin deficiency
  - Fulminant liver failure
  - Chronic hepatitis
  - Metabolic liver disease
  - Cirrhosis of unknown origin

WHEN TO REFER

- Unexplained jaundice
- Direct hyperbilirubinemia at any age
- Persistence of abnormal liver tests
- Jaundice with hepatomegaly or splenomegaly

WHEN TO ADMIT

- Jaundice in an ill patient
- Feeding intolerance and dehydration
- Inpatient management of underlying conditions
- Impending acute liver failure

COMPLICATIONS

- If the underlying liver condition which results in hyperbilirubinemia is not diagnosed early and treated properly, it may lead to hepatic failure.

PROGNOSIS

- Prognosis depends on the underlying cause of direct or indirect hyperbilirubinemia.

PREVENTION

- Hepatitis A and B can be prevented by vaccinating all children.

DEFINITION

- *Arthralgia* is joint pain, the subjective experience of pain referable to a bony articulation.
  - In a young child, sensation of pain might be inferred from the patient's refusal to move a particular extremity or joint.
- *Arthritis* is an inflamed joint.
  - Redness
  - Warmth
  - Swelling
  - Tenderness
  - Pain with motion
  - Can be accompanied by loss of motion
- All that is arthralgia is not arthritis.
- *Arthropathy* is any disease of a joint, no matter its cause.

HISTORY

- A complete history is indispensable in the initial assessment of joint pain.
- A common symptom is loss of motion in a joint, with or without obvious swelling.
  - Further clues are time of day that stiffness occurs and its duration.
  - In juvenile idiopathic arthritis (JIA), patients typically experience joint stiffness when waking up in the morning (lasting 30 minutes to several hours).
  - Hypermobility syndrome and other mechanical, noninflammatory conditions cause pain and stiffness at the end of a vigorous day.

PHYSICAL EXAMINATION

- The physical examination can substantiate or alleviate suspicions raised during history taking.
- Distinguishing among arthritis, arthralgia, periarticular pain, and myalgia is essential.
- In systemic-onset JIA, in addition to fever, other distinguishing signs are
  - Rash
  - Mucous membrane involvement
  - Lymph node inflammation or enlargement
- See Differential Diagnosis for condition-specific physical examination findings.

DIFFERENTIAL DIAGNOSIS

- Differential diagnosis should begin by determining whether disease is inflammatory or noninflammatory.
- Inflammatory disease can result from rheumatic or nonrheumatic causes.
- Noninflammatory diseases may result from
  - Trauma
  - Repetitive stress
  - Congenital or developmental abnormalities
  - Other mechanical causes

Rheumatic Diseases

- JIA, previously called juvenile rheumatoid arthritis.
  - Oligoarticular.
    - Involves ≤4 joints.
    - Usually involves large joints.
    - Can cause growth abnormalities.
    - Positive antinuclear antibody (ANA) carries an increased risk of eye involvement with iridocyclitis.
  - Polyarticular.
    - Involves >4 joints.
    - Affects large and small joints.
    - Some patients have serum immunoglobulin M rheumatoid factor and typically more symmetric joint disease, akin to adult onset rheumatoid arthritis.
  - Systemic-onset disease (sometimes called *Still disease*).
    - Marked by high, spiking fevers.
    - Typical salmon-pink, maculopapular, evanescent rash.
    - Lymph node, spleen, and liver enlargement.
    - Subcutaneous nodules.
    - Anemia.
    - General malaise.
    - Systemic findings can precede onset of joint involvement.
  - Arthritis must be present for ≥6 consecutive weeks to establish diagnosis of any of the subgroups of JIA.
  - Among patients with any subtype of JIA
    - The clinician may glean only a history of ill-defined arthralgias and stiffness.
    - Physical examination may reveal
      - Contractures of the elbows, knees, and wrists
      - Limitation of cervical motion
      - Iridocyclitis and keratopathy
- Ankylosing spondylitis (spondyloarthropathy).
  - Can involve large joints of the lower extremities or entheses (insertion of tendon or ligament into a bone).
  - At onset, there may be no axial disease.
  - Small joint involvement is often asymmetric when present, and dactylitis (sausage digits) can occur if several joints and intervening soft tissues in a single finger or toe are swollen.

- Classic presentation: sacroiliac involvement in late adolescence.
  - Seen on radiographs or magnetic resonance imaging
  - Pain elicited on palpation or compression over the joint
- Similar pattern of asymmetric large joint and sacroiliac disease can be seen in patients with inflammatory bowel disease.

- Children with psoriasis, or with a first-degree relative with psoriasis, may have arthritis with a predisposition for large joints, sacroiliac disease, and, occasionally, dactylitis.
- Systemic lupus erythematosus.
  - Multisystem disease that can involve almost any organ in the body.
  - Arthralgias and, sometimes, arthritis are not uncommon and may be the presenting symptom.
- Juvenile dermatomyositis.
  - Characterized more by skin rashes and muscle inflammation and weakness than joint disease
  - Can also be accompanied by joint pain or swelling in some cases
- Sjögren syndrome, scleroderma, mixed connective tissue disease.
- Systemic autoinflammatory syndromes (often called *periodic fever syndromes*).
  - Familial Mediterranean fever
  - Tumor necrosis factor (TNF)-receptor–associated periodic syndrome
  - Hyperimmunoglobulin D syndrome
  - Cryopyrin-associated periodic syndrome
- Kawasaki disease.
- Henoch-Schönlein purpura and other types of vasculitis.

Infectious and Postinfectious Arthritis

- Acute bacterial infection (septic arthritis)
  - A medical emergency.
  - Usual manifestation is rapid onset of pain in a joint, typically accompanied by fever.
  - Joint is red, warm, swollen, and exquisitely tender to palpation or with movement.
  - With infection of the hip, redness, warmth, and swelling may not be apparent, and pain may be referred to the knee.
- Osteomyelitis: acute bone infection
  - If a long bone next to a joint (eg, the distal femur and knee) is infected
    - The patient may describe pain in the joint.
    - Sterile effusion may be present.
  - Although unusual, infection can directly invade the joint space from the bone, particularly in young children.
- Systemic bacterial infections
  - Notably caused by *Neisseria gonorrhoeae* and *Neisseria meningitidis*
  - Can produce arthritis, although organisms not usually isolated from the joint
- Diskitis
  - Disorder characterized by back pain and tenderness over the spinous process contiguous to the involved disk space
    - Causes joint pain, sometimes with low-grade fever, but often with none.
    - *Staphylococcus aureus* has been isolated from the blood and disk space in some instances, but often, no culture-proven cause can be found.
    - Presentation can involve sensory and motor complications.
    - Epidural abscess must be considered in the differential diagnosis.
- *Borrelia burgdorferi* (tick-borne spirochete responsible for Lyme disease)
  - Recurrent attacks of inflammation of the large joints (85%–90% of cases involve the knee).
  - Each recurrence usually lasts 1 or 2 weeks.
  - Symptoms may persist for several months; chronic arthritis of the knee has been reported.
- Viruses that can affect synovial tissue
  - Rubella.
  - Mumps.
  - Varicella.
  - Parvovirus.
  - Adenovirus.
  - Epstein-Barr virus.
  - HIV.
  - Manifestations of the viral syndrome (rash, fever, mucous membrane involvement) usually precede joint involvement.
  - Infectious hepatitis can cause arthritis before overt hepatic involvement.
  - Rubella immunization is associated with arthralgia and arthritis in as many as 3% of children who receive the vaccine, although rarely, if ever, with any sequelae.
- Less common infections involving joints
  - Leptospirosis
  - Tularemia
  - Rocky Mountain spotted fever
  - Rat-bite fever
  - Mycobacteria and fungal agents, particularly in immunocompromised individuals

- Reactive arthritis
  - Previously called *Reiter syndrome.*
  - Triad of urethritis, conjunctivitis, and arthritis.
  - Often triggered by an episode of enteritis.
  - Diagnosis depends on excluding direct infectious causes of the inflammation.
  - Arthritis predominantly occurs in large joints.
- Transient synovitis of the hip
  - Previously called toxic synovitis
  - Can cause arthralgia, arthritis, or both
- Acute rheumatic fever
  - Follows an infection with group A streptococcus, usually pharyngitis, typically by about 2 or 3 weeks.
  - Diagnosis is made using the Jones criteria.
    - Migratory arthritis or arthralgias
    - Fever
    - Carditis
    - Rash (erythema marginatum)
    - Central nervous system involvement
    - Subcutaneous nodules
    - Elevated acute phase reactants
    - Prolonged PR interval
- Poststreptococcal reactive arthritis
  - May occur after a streptococcal infection in the absence of other findings.
  - The arthritis may be more severe, and this may occur sooner after the preceding illness than is the case with rheumatic fever.

Noninflammatory Causes of Joint Pain

- Trauma causing fractures, dislocations, cartilage, ligamentous, or tendon injury, or other soft tissue damage
  - Common in children and can cause joint pain, depending on the location of the injury.
  - A careful history can usually provide information about the mechanism of the event.
- Physical abuse (non-accidental trauma)
  - Consider whenever signs of trauma are evident.
  - Accidents representing neglect on the part of parents or guardians need to be pursued.
  - Any suspicious history or circumstance demands complete investigation.
- Patellar femoral pain syndrome (also called chondromalacia patellae)
  - Knee pain usually related to activity.
  - Child may report symptoms of "locking" with prolonged sitting or "giving way" with extensive standing.
- Stress fractures
  - Uncommon in children
  - Should be considered in an athlete with chronic bone or joint pain
- Osgood-Schlatter disease, Sever disease, and other forms of apophysitis
  - Occur only in skeletally immature individuals who have a repetitive or acute injury to the apophysis
- Slipped capital femoral epiphysis
  - Seen only in skeletally immature children.
  - Capital femoral epiphysis is displaced from the femoral neck.
  - May manifest as hip or, sometimes, thigh or knee pain.
  - Seen typically in overweight adolescents.
- Growing pains
  - Discomfort in the lower limbs and joints.
  - Not associated with warmth, swelling, or limitation of movement of the affected joints.
  - Often worse at night.
  - Pain in the mornings is rare.
  - Children have normal daytime activities.
- Hypermobility syndrome
  - Increased joint laxity with vigorous activity; especially with extremes of joint flexion and extension, patient can experience significant arthralgia.
  - Diagnosis is made by physical examination and observation of ≥3 of the following 5 signs:
    - Hyperflexion of the wrist, bringing the thumb in contact with the volar surface of the forearm
    - Hyperextension of the fingers to parallel with the forearm
    - Hyperextension of the elbow to at least -10°
    - Hyperextension of the knee to at least -10°
    - Hyperflexion of the spine such that with forward flexion, the palms can be placed flat on the ground with the feet together and without flexing the knees
- Marfan and Ehlers-Danlos syndromes
  - Can cause pronounced hypermobility
- Juvenile primary fibromyalgia syndrome
  - Consider in an adolescent with chronic diffuse pain and fatigue without evidence of rheumatic disease on examination or laboratory studies.

- Diagnostic criteria include
  - Widespread pain for several months
  - Presence of specific tender points on examination
  - Presence of severe fatigue and non-restorative sleep
- These children often also have headaches, depression or anxiety, a sense of cognitive impairment, numbness or tingling or stiffness in the limbs, irritable bowel symptoms, or other complaints.

- Complex regional pain syndrome
  - Presents with localized limb pain, sometimes after an injury, but out of proportion to examination findings.
  - Concurrent sleep disruption and psychological conditions are also common.
- Congenital syphilis
  - In infants, painful bony lesions and refusal to move the involved limb (*Parrot pseudoparalysis*), along with other associated stigmata.
  - Adolescents born with this disease can develop bilateral knee effusions (*Clutton joints*).

Other Causes

- Hematologic disorders.
  - Hemophilia
  - Sickle cell disease
    - Hand-foot syndrome: type of vasoocclusive crisis that is a common initial presentation in children 1–4 years of age
- Osteoid osteomas.
  - Benign bone tumors most often seen in older children and teens
- Pigmented villonodular synovitis.
  - Benign neoplasm of the synovium, which can present with joint pain and swelling
- Leukemia is the most common malignant condition to present with bone or joint pain, although lymphoma, neuroblastoma, and Ewing and other sarcomas can also cause these symptoms.

LABORATORY EVALUATION

- With concern for rheumatic inflammatory arthritis
  - Erythrocyte sedimentation rate
  - C-reactive protein
  - Complete blood cell count
  - ANA test
    - Among children with JIA, those with oligoarticular disease are most likely to have a positive result.
  - Rheumatoid factor titer
    - Present in only a small subset of children with polyarticular JIA
  - Serum immunoglobulin levels
- With concern for septic arthritis, blood cultures may yield growth of the organism, occasionally in the absence of a positive joint fluid culture result.

IMAGING

- Radiographs of joints are not routinely helpful with diagnosis.
- They can be useful in evaluating surrounding soft tissue and bones.

DIAGNOSTIC PROCEDURES

- Arthrocentesis for septic arthritis and analysis of the fluid for
  - Appearance (opaque).
  - Viscosity (usually low).
  - Mucin clot (friable).
  - Cell count (>100,000 leukocytes/mm with ≥80% polymorphonuclear cells).
  - Glucose (usually low, much less than in serum).
  - Protein (high).
  - A portion of the fluid should be Gram stained to assess for bacterial organisms.
  - Cultures can direct definitive antimicrobial therapy.
    - *S aureus* and *Streptococcus* organisms are likely to be the causative organisms.

TREATMENT APPROACH

- Management focuses on
  - Subduing inflammation
  - Preserving normal range of joint motion and strength
- *Septic arthritis* demands immediate arthrocentesis for diagnosis and therapy.
  - After joint aspiration and establishment of strong suspicion of purulent arthritis, the child should be hospitalized and appropriate intravenous (IV) antibiotic therapy initiated.
  - Prompt, aggressive therapy usually brings about recovery without adverse side effects, although some foci, such as the hip joint, can remain persistent problems.
- Surgery is used mostly in joint reconstruction or prosthetic replacement.

SPECIFIC TREATMENT

JIA

- Nonsteroidal anti-inflammatory drugs (NSAIDs) are used as initial therapy.
- For children with JIA, methotrexate plays a central role in therapy beyond NSAIDs.
- Other long-acting agents include
  - Anti–TNF-α agents
  - Anti–interleukin-1 (IL-1) drugs in systemic-onset JIA
- Other immunomodulatory agents, such as sulfasalazine, leflunomide, and hydroxychloroquine, may also be used in some patients.
- Many patients who have resistant joint inflammation or high-risk phenotypes benefit from biologic agents, including anti–TNF-α agents and IL-1 or IL-6 antagonists.
- Systemic corticosteroids are used less frequently and at lower doses than in the past.
  - For patients with oligoarticular disease, especially those with a single persistently active joint, intra-articular corticosteroids (eg, triamcinolone hexacetonide) can be effective.
- There may be a role for surgical treatment of long-standing joint damage from chronic or severe inflammatory arthritis or mechanical derangements.

Bacterial Infection

- Bacterial infection of the joint space or bone should be promptly identified and treated with IV antibiotics.
  - Pending culture results, treatment should cover *S aureus* and *Streptococcus* organisms.
- With *B burgdorferi* infection (Lyme disease), amoxicillin seems to shorten the course of the rash and perhaps attenuate the arthritis; NSAID therapy relieves the symptoms.
- Sometimes surgical intervention is necessary for establishing a diagnosis, as in synovial biopsy for atypical infections or bone biopsy for osteomyelitis.

Noninflammatory Joint Pain

- Chondromalacia patellae
  - Exercises that strengthen the quadriceps femoris and adductor muscles can produce marked improvement.
  - NSAIDs and analgesics may also be administered for symptomatic relief.
- Osgood-Schlatter disease, Sever disease, and other forms of apophysitis
  - Treated with activity modification, rehabilitation, and analgesia as needed
- Growing pains
  - A bedtime dose of an NSAID can help alleviate pain until it resolves by itself.
- Hypermobility syndrome
  - Treated with NSAIDs and reassurance.
  - For some patients, exercises to increase muscle strength and tone can be beneficial.
- Juvenile primary fibromyalgia syndrome
  - Treatment should be multidisciplinary.
    - Patient and family education
    - Exercise
    - Psychological interventions, such as cognitive behavioral therapy
  - Some patients benefit from medications.
    - Nonnarcotic analgesics
    - Low-dose tricyclic antidepressants
    - Other antidepressants
    - γ-Aminobutyric acid agonists, such as gabapentin or pregabalin
- Complex regional pain syndrome
  - Treatment consists of aggressive physical and occupational therapy, psychological and behavioral therapies, and, sometimes, pharmacotherapy or localized interventions, such as nerve blocks.

Management of Psychological Aspects of Joint Disease

- In children with ongoing joint problems, issues related to chronic pediatric disease must be addressed.
- The child may be unable to keep up with peers in physical activity and may be faced with having to make many health care visits, resulting in school absences.
- Many physicians think that environmental stress, in addition to the stress caused by the disease, can exacerbate various chronic conditions, and such may occur in children with JIA.
- Children faced with hospitalization for an acute problem, such as septic arthritis, are exposed to all the complications of being taken out of their family and school environment, as well as having to deal with an institutional setting.
- Children with ongoing joint disease, even those with only a mild disability, should be provided with the services of a specialized social worker, counselor, or psychologist.

- Family resources (emotional and financial) need to be assessed and support provided when needed.
- Discussion or support groups composed of these children and their families can be helpful because they offer an opportunity to compare experiences and coping mechanisms.
- Attention to the physical dimension alone does not provide adequate care in these diseases.
- A functionally minor disability can cause major problems of body image and feelings of lack of independence that must be dealt with appropriately.

WHEN TO REFER

- Orthopedics
  - Fracture
  - Ligamentous or cartilage injury to joint
  - Continuous pain in a joint with deformity
- Rheumatology
  - Suspicion of JIA or other rheumatologic disorder
- Infectious diseases
  - Septic arthritis
  - Lyme disease; other spirochetal infection
  - Osteomyelitis
- Hematology
  - Sickle cell disease
  - Hemophilia
- Gastroenterology
  - Joint symptoms associated with inflammatory bowel disease
- Occupational or physical therapy
  - Joint disease complicated by contractures, weakness, poor function
  - Hypermobility syndrome
  - Pain amplification syndromes
- Mental health
  - Suspicion of somatization or conversion disorder

WHEN TO ADMIT

- Fracture requiring open fixation or traction.
- Systemic-onset JIA with macrophage activation syndrome.
- Septic arthritis.
- Osteomyelitis.
- Severe sickle cell pain crisis.
- Admit to rehabilitation if inadequate response to outpatient occupational or physical therapy.

COMPLICATIONS

- Long-term psychosocial sequelae also may develop from chronic joint problems.

Juvenile Idiopathic Arthritis

DEFINITION

- Juvenile idiopathic arthritis (JIA) is an uncommon collection of clinical syndromes that share the feature of chronic childhood arthritis.
  - Previously referred to as *juvenile rheumatoid arthritis* or *juvenile chronic arthritis.*
  - Term refers to any child or adolescent <16 years who has
    - Persistent arthritis of ≥1 joints.
    - Condition lasting for >6 weeks.
    - All other diseases have been excluded.
  - JIA is classified further into 7 subtypes.
    - Most patients fit into systemic onset, oligoarthritis, or polyarthritis based on the clinical course over the first 6 months of illness.
- Presence of arthritis or inflammation in joint is an absolute criterion for diagnosing JIA.
- *Arthritis* is defined as presence of
  - Intra-articular swelling or effusion *or*
  - ≥2 of
    - Joint pain or tenderness with motion
    - Limitation of joint motion
    - Increased warmth overlying the joint
- *Arthralgia* is joint pain, a relatively frequent symptom in children.
- Rheumatologic disorders with arthritis.
  - Juvenile ankylosing spondylitis and other spondyloarthropathies can present as a subtype of JIA at onset, especially in an older child who is human leukocyte antigen (HLA)-B27 positive.
  - Acute rheumatic fever has seen a resurgence in the past few decades.
    - Patients can experience arthralgia and arthritis, classically characterized as migratory.
  - Systemic lupus erythematosus (SLE) has arthritis as one of its major manifestations.
    - Differentiated from JIA by other systemic features and specific laboratory test abnormalities.
    - Sex distribution is equal in younger children, but a female preponderance is found after puberty.
    - Patients with SLE may have arthralgia without arthritis.
  - Dermatomyositis is characterized by inflammatory muscle involvement rather than by arthritis.
    - Joint inflammation and contractures may be present.
  - Scleroderma is occasionally associated with arthritis.
    - Classic dermatologic and other manifestations distinguish it from JIA.

SIGNS AND SYMPTOMS

General

- The presence of arthritis or inflammation within the joint is an absolute criterion for diagnosing JIA.
- Younger children rarely complain of joint pain but may
  - Become irritable.
  - Stop walking or using an extremity.
  - Regress in their behavior.
- Other symptoms include
  - Decreased appetite
  - Malaise
  - Inactivity
  - Morning stiffness
  - Nighttime joint pains
  - Failure to thrive
- Features that may be present in children who have chronic arthritis (varying with the subtype) include
  - Fever
  - Rash
  - Lymphadenopathy
  - Hepatosplenomegaly
  - Polyserositis
  - Subcutaneous (rheumatoid) nodules
  - Vasculitis
  - Growth retardation
- Pattern and number of involved joints are important in classifying the disease.

Systemic Onset JIA (Still Disease)

- The hallmark of systemic onset JIA is its extra-articular manifestations.
- The eventual presence of arthritis is still necessary to confirm diagnosis.
- Systemic features may persist for months and occur or recur independently of the arthritis.
  - Daily intermittent fevers.
    - Rectal temperature as high as 40°C–41°C (104°F–106°F).
    - Most often in the afternoon.
    - Returning to normal or subnormal levels (known as a *quotidian fever pattern*).
    - Children frequently complain of myalgias or arthralgias when they are febrile, but they may have few symptoms when the fevers resolve.

- Evanescent, salmon-colored rash often accompanies fevers.
  - Lesions are small macules or papules.
  - Frequently with central clearing.
  - Often appear in areas of increased heat (eg, axilla).
- Mild abrasion of unaffected skin can precipitate appearance of the rash (Koebner phenomenon).
- Polyserositis in the form of pericarditis or pleuritis.
  - These serosal effusions are rarely symptomatic or clinically significant.
- Enlargement of the lymph nodes, liver, and spleen may suggest the presence of cancer.
- Arthritis may occur at any time after the onset of disease.
  - In some, it appears only days to weeks after the systemic signs occur.
  - Tends to be polyarticular, involving large and small joints.
  - Can be persistent, destructive, and severe.

- Clinical course is extremely variable.
  - A single systemic episode may last weeks to months, with few joint problems.
  - Multiple systemic episodes may precede development of arthritis.
  - Can be oligoarticular but is more commonly polyarticular.
- Macrophage activation syndrome.
  - An unusual but potentially fatal complication of systemic onset JIA.
  - Rapidly progressive and difficult to distinguish from a flare of JIA.
  - Characterized by
    - Intravascular consumption coagulopathy
    - Dramatically elevated ferritin (>10,000 ng/mL)
    - Paradoxically decreased erythrocyte sedimentation rate (ESR)
    - Decreased fibrinogen
    - Increased triglyceride levels
    - Pancytopenia
    - Hepatic failure
  - Bone marrow biopsy may be helpful in confirming diagnosis.
  - Rapid intervention is necessary.

Polyarticular JIA

- Systemic features in polyarticular JIA are usually mild and include
  - Low-grade fever
  - Easy fatigability
  - Slowing of growth
    - Growth problems may be local (eg, micrognathia) or generalized.
    - Can occur regardless of whether the child receives corticosteroid treatment.
  - Discrepancies between height and weight can help with diagnosis.
    - For example, children who have polyarticular JIA may be of low weight for height, whereas children who have systemic onset JIA tend to be average in weight for height.
  - Chronic uveitis.
- Arthritis symptoms
  - Most often chronic, symmetric, and involving ≥5 joints.
  - Any joint can be affected.
  - Nearly all children have wrist involvement; small joint involvement of hands and feet is common.

Rheumatoid Factor (RF)–Positive Polyarticular JIA

- Patients with immunoglobulin M (IgM) RF-positive polyarticular JIA are
  - Most often >8–10 years old
  - More likely to be girls than boys
  - Similar clinically to patients with adult rheumatoid arthritis
- Arthritis symptoms are
  - Severe
  - Rapidly progressive
  - Erosive
  - Crippling
  - Subcutaneous rheumatoid nodules
  - Rheumatoid vasculitis

RF-Negative Polyarticular JIA

- Children with IgM RF-negative polyarticular JIA are usually younger.
- Because their arthritis starts earlier, it can lead to deformities and problems as a result of
  - Tendency to develop flexion contractures
  - Subluxations at the involved joints
- Compared with adults, hand involvement affects interphalangeal joints more often than metacarpophalangeal joints.
- Ulnar deviation of the fingers is much less common in children.
- Ulnar deviation and subluxation at the wrist may occur.
- More frequently seen in children.
  - Flexion contractures
  - Boutonniere (buttonhole) deformities
  - Radial deviation of the fingers

- Arthritis of the apophyseal joints of the cervical spine is common.
  - Can lead to rapid and significant limitation of extension and rotation
- These children are at the highest risk for local and generalized growth problems.

Oligoarticular JIA

- Involves ≤4 joints, most often large (eg, knee, ankle, elbow).
- Typically asymmetric in distribution.
- Important in distinguishing this form of JIA.
  - Pattern and course of joint involvement
  - Number of joints involved
- Systemic features are infrequent and mild.
- Oligoarticular JIA can be subdivided further into persistent and extended oligoarticular subtypes.
- Persistent oligoarthritis.
  - Occurs typically in girls <6 years.
  - Involves the large joints.
  - Higher risk for chronic uveitis, particularly when positive for antinuclear antibodies (ANA).
  - Systemic signs and symptoms, except for uveitis, are few.
  - These children generally function well and only rarely complain of significant pain.
  - Little erosive joint damage occurs, even though patients may have ongoing arthritis for many years.
  - At risk for long-term problems, including
    - Leg-length discrepancies (a complication of ongoing asymmetric knee joint involvement)
      - Growth centers around the arthritic knee can become more active because of the inflammatory-associated hyperemia, resulting in increased growth of that leg.
    - Muscle atrophy
      - As a result of changes in the child's biomechanics, decreased quadriceps mass on the affected side is frequently found.
- Extended oligoarthritis.
  - ≤4 joints involved within first 6 months of disease.
  - At different times after the initial 6 months, children develop arthritis in more joints.
  - Genetic makeup.
    - Higher frequency of HLA-DR1 than in persistent oligoarthritis
  - Higher occurrence of erosive disease than in persistent oligoarthritis.
  - Additionally involved joints are often
    - Wrists
    - Fingers
    - Other smaller joints
  - Chronic uveitis still occurs, although less frequently.

Enthesitis-Related Arthritis

- A newer classification that includes children who previously were classified as late-onset oligoarthritis.
- Complaints and findings of enthesitis (inflammation of the attachment of a tendon, ligament, fascia, or capsule to bone) are a hallmark of this group and may predate joint problems.
- Subgroup includes children with
  - Arthritis and enthesitis *and*
  - ≥2 of
    - Sacroiliac joint pain or inflammatory spinal pain (or both)
    - Presence of HLA-B27
    - History of relatives with HLA-B27–associated disease
    - Anterior uveitis usually associated with pain, redness, or photophobia
    - Onset of arthritis in a boy >8 years
- More frequently occurs in the lower extremities, involving the knees and ankles; occasionally in toes (resulting in so-called *sausage toe,* or dactylitis).
- Patients may progress to
  - Ankylosing spondylitis
  - Reactive arthritides
  - Arthritis associated with inflammatory bowel disease

Psoriatic Arthritis

- An additional classification subtype of JIA.
- Similar to enthesitis-related arthritis in that large joint inflammation, enthesitis, and dactylitis are often found.
- Psoriasis must be present in the patient or in family members.
  - Thus, a child can have psoriatic arthritis in the absence of skin disease.
  - Psoriatic rash can appear some time after the onset of joint disease.
- Pitting of the fingernails or toenails can identify psoriatic arthritis in the child with characteristic musculoskeletal findings but no skin eruption.

Undifferentiated Arthritis

- Children who do not meet the criteria for ≥1 subtype

DIFFERENTIAL DIAGNOSIS

- Diseases to be considered in the differential diagnosis of JIA
  - Rheumatic diseases of childhood
    - Autoinflammatory diseases
      - Familial Mediterranean fever
      - Tumor necrosis factor (TNF)-α–associated periodic fever syndrome
      - Hyper-IgD syndrome
      - Muckle-Wells syndrome
      - Neonatal-onset multisystem inflammatory disease (also known as *chronic infantile neurologic, cutaneous, and articular syndrome*)
      - Familial cold autoinflammatory syndrome
    - Acute rheumatic fever
    - SLE
    - Juvenile ankylosing spondylitis
    - Polymyositis and dermatomyositis
    - Vasculitis
    - Scleroderma
    - Mixed connective-tissue disease/overlap
    - Serum sickness
    - Kawasaki disease
    - Henoch-Schönlein purpura
    - Behçet syndrome
    - Wegener granulomatosis
    - Postinfectious reactive arthritis
    - Reactive arthritis
    - Reflex neurovascular dystrophy/reflex sympathetic dystrophy (complex regional pain syndrome type II)
      - Deserves consideration in children who have a hot or cold, pale, painful, and exquisitely sensitive (allodynia) extremity that they refuse to move, particularly when a premorbid history of trauma (often minor) is found
    - Fibromyalgia syndrome
- Infectious diseases
    - Bacterial arthritis
      - Must be considered if the child has a single inflamed joint.
      - *Neisseria gonorrhoeae,* particularly in adolescence.
      - Staphylococci may be found at any age.
      - Lyme disease (*Borrelia burgdorferi* infection) in endemic areas.
    - Viral or postviral arthritis
      - Parvovirus
      - Rubella
      - Hepatitis B
    - Fungal arthritis
    - Osteomyelitis
    - Postinfectious reactive arthritis
      - From a gastrointestinal bacterial infection (eg, *Shigella, Salmonella, Campylobacter, Yersinia* organisms)
    - Lyme disease
  - Neoplastic diseases
    - Leukemia.
    - Lymphoma.
    - Neuroblastoma.
    - Primary bone tumors.
    - Although arthritis is uncommon and usually transient, complaints of pain that are out of proportion to physical findings, particularly nighttime pain, are common and potentially important clues.
  - Noninflammatory disorders
    - Trauma
    - Avascular necrosis syndromes
    - Osteochondroses
    - Slipped capital femoral epiphysis
    - Diskitis
    - Patellofemoral dysfunction (chondromalacia patellae)
    - Toxic synovitis of the hip
    - Overuse syndromes
  - Hematologic disorders
    - Sickle cell disease
    - Hemophilia
  - Miscellaneous
    - Osgood-Schlatter disease
    - Inflammatory bowel disease
    - Chronic recurrent multifocal osteomyelitis
    - Sarcoidosis
    - Collagen (connective tissue) disorders (eg, Ehlers-Danlos syndrome, Marfan syndrome)
    - Growing pains
    - Psychogenic arthralgias (conversion reactions)
    - Hypermobility syndrome
    - Villonodular synovitis
    - Foreign-body arthritis

DIAGNOSTIC APPROACH

- Because the diagnosis of JIA is based on clinical findings, history and physical examination are paramount.
- The hallmark of JIA is its chronic nature, and the best initial strategy is often careful, watchful waiting.

- The primary care physician can avoid mislabeling other transient entities as JIA by
  - Meeting the criterion of sustained arthritis (>6 weeks)
  - Excluding other possible diseases

LABORATORY FINDINGS

- No unique or specific diagnostic laboratory tests yet exist.
- Systemic onset JIA.
  - High leukocyte count, with predominance of band forms and polymorphonuclear leukocytes.
  - Most patients are anemic.
  - Thrombocytosis.
  - Significant increases of acute phase reactants (eg, ESR, C-reactive protein level).
  - RF and ANA test results are rarely positive.
  - Serum immunoglobulin and complement levels are usually normal.
    - — May be elevated, reflecting the degree of inflammation
    - — Sometimes indicate a vasculopathy and an intravascular consumption coagulopathy
      - With intravascular consumption coagulopathy, need to rule out macrophage activation syndrome
- RF-positive polyarticular JIA.
  - Cyclic citrullinated protein can be used to assess disease severity and potential for joint destruction.
  - An elevated serum level would serve as reason to institute early and aggressive therapy.
- Persistent oligoarthritis.
  - Few laboratory abnormalities will be found except for positive ANA.
    - — When positive, the ANA titer is typically low.
  - Mild increases in leukocyte count and ESR or low-grade anemia may be observed, but these tests are most often within reference range.
  - HLA-DR5 gene markers appear to confer increased susceptibility for persistent oligoarthritis; HLA-DR1 and HLA-DR4 are underrepresented in this group.
- Enthesitis-related arthritis.
  - Infrequently, laboratory tests are abnormal.
  - Mild to moderate increase in ESR is common.

DIAGNOSTIC PROCEDURES

- If any question exists as to an intra-articular septic process, arthrocentesis must be performed to establish the diagnosis.

TREATMENT APPROACH

- JIA is a chronic illness, and no current mode of therapy is curative.
- The patient's management should be individualized for
  - Disease subtype
  - Extent of activity
  - Clinical course to date
  - Family situation
- Pharmacologic therapy is only one aspect of treatment.
- Drug therapy is not yet curative but can suppress the inflammatory activity in many children.
- 5 major categories of drug therapy are available.
  - Nonsteroidal anti-inflammatory drugs (NSAIDs)
  - Disease-modifying antirheumatic drugs (DMARDs)
  - Corticosteroids
  - Immunosuppressive drugs
  - Agents with immune- and cytokine-modulating effects (biological agents)
- A multidisciplinary team approach is the most effective approach.
- The goal of therapy is to attain the highest possible level of physical and psychologic function for the child.
- In addition to an attentive and understanding primary care physician, the patient and family need
  - Family counselor, social worker, and psychologist or similar mental health professional to help them adjust to this chronic illness
    - — Feelings of denial, guilt, and frustration at the time of the diagnosis and throughout the course of the disease are common.
    - — Siblings frequently find it difficult to cope with the special and extensive treatment the affected child may receive.
- Periodic depression and anger are frequent, especially in the early stages, and again as the patient enters adolescence.
- Poor maternal function, maternal depression, and social isolation are risk factors for poor psychosocial outcomes; a sense of control and mastery are important positive factors.
- Most children with JIA can do well in school; thus, all efforts should be made to keep them enrolled.
  - Some school adjustments may be necessary, such as different transportation or physical education (or both) and allowing extra time between classes.

- 2 sets of books, one for school and one for home, reduce the work of carrying them.
- The primary care physician or pediatric rheumatology team may have to advocate within the school to ensure services.

- Preparation for eventual independent living and vocations must begin in childhood to reduce potential barriers.
  - Anticipatory guidance about transitional issues should start in childhood and early adolescence.
- The child with mild disease and a hidden disability may have problems coping, adapting, and trying to accomplish unrealistic goals in a society that does not recognize the disability.
- Any chronic illness imposes many additional stresses on the entire family.

SPECIFIC TREATMENTS

NSAIDs

- NSAIDs currently approved by the US Food and Drug Administration (FDA) for use in children.
  - Individual responses to NSAIDs vary widely, and if a child does not improve within 4–6 weeks, trying a different NSAID is reasonable.
  - Salicylates.
    - No longer the initial NSAIDs of choice because of concerns about Reye syndrome and short half-life.
    - Other agents have emerged that are essentially equivalent in efficacy and toxicity.
  - Indomethacin.
  - Tolmetin sodium.
  - Naproxen.
  - Ibuprofen.
  - Celecoxib.
  - Meloxicam.
- NSAIDs not approved by the FDA for use in children.
  - Diclofenac sodium
  - Fenoprofen
  - Flurbiprofen
  - Ketoprofen
  - Phenylbutazone
  - Pirprofen
  - Piroxicam
  - Meclofenamate sodium
  - Sulindac
- NSAIDs available in liquid form for younger children who have trouble swallowing pills.
  - Naproxen
  - Ibuprofen
  - Indomethacin
  - Meloxicam
- Cyclooxygenase-2 (COX-2) selective inhibitors decrease the prostaglandin production that mediates inflammation, in a gastro-protective manner.
  - Reduces the risk of gastric erosion or ulcer formation, or both.
  - As a result of cardiovascular safety questions, many were removed from the market.
  - Celecoxib remains available in the United States.
  - Meloxicam is predominantly COX-2 selective and is available in a generic preparation.

DMARDs and Cytotoxic/ Immunosuppressive Drugs

- If a child does not quickly respond to NSAID therapy alone or is in a high-risk category, more aggressive interventions are necessary.
- Moving quickly to DMARDs or biological agents, as well as performing intra-articular corticosteroid injections, appears to eliminate inflammation with great effectiveness.
- Methotrexate.
  - Essentially replaced intramuscular and oral gold, D-penicillamine, and hydroxychloroquine as primary second-line agent of JIA treatment.
  - Competitive inhibitor of dihydrofolate reductase, which exerts anti-inflammatory and immunosuppressive effects on arthritis.
  - Efficacy and dose response have been well established.
  - Subcutaneous administration results in high and consistent blood levels and may provide control of the arthritis if oral dosing is ineffective.
  - Hepatic, bone marrow, gastrointestinal, pulmonary, and teratogenic adverse effects may result.
    - To detect liver or hematopoietic adverse effects, laboratory monitoring every 4–8 weeks is suggested.
    - Administration of folic (or folinic) acid may decrease some of methotrexate's adverse effects, such as nausea and oral ulcers.
- Leflunomide.
  - Immunosuppressive agent that inhibits pyridine synthesis and suppresses TNF-α–induced cellular responses.
  - Shown to have beneficial effects similar to methotrexate.
  - Teratogenic effects are possible.
  - Requires ongoing monitoring
  - Not FDA approved for use in treating JIA.
- Sulfasalazine.

- Has seen a resurgence but should not be used in anyone
  - Who is sensitive to sulfa drugs or salicylates
  - Whose renal or hepatic function is impaired
  - Who has such conditions as glucose-6-phosphate dehydrogenase deficiency
- Adverse effects caused by sulfasalazine include
  - Rashes
  - Nausea
  - Vomiting
  - Dyspepsia
  - In boys, a reversible decrease in sperm count
  - Bone marrow depression (rare)

- Other immunosuppressive agents occasionally administered in specific patients, but not currently the standard, include
  - Intravenous (IV) immunoglobulin
  - Azathioprine
  - Chlorambucil
  - Cyclophosphamide
  - Cyclosporine
  - Thalidomide

Biological Agents

- Considered standard to add a TNF-α blocker to the regimen of any child with JIA
  - Who has not responded to previously administered DMARD therapy
  - When tapering the dose of corticosteroids is not possible without precipitating a flare of the disease
- Testing for tuberculosis is recommended before starting because these agents can interfere with immune response and cause reactivation of latent tuberculosis.
- Adverse effects include
  - Injection site pain or reactions
  - Increased risk of infection
  - Possible increased risk of other autoimmune conditions or neoplasms
- Long-term effects are not yet known.
- Etanercept, adalimumab, and infliximab.
  - Block activity of TNF-α (a major proinflammatory cytokine).
  - Etanercept and adalimumab are approved for use in children with JIA.
  - Demonstrated dramatic improvements in condition of children and adults with arthritis
  - A child who has not responded or has had an adverse effect to one agent may still respond to another because each is slightly different.
- Interleukin (IL)-1 and IL-6 are cytokines that play a significant role in JIA treatment.
  - Systemic onset JIA is more of an IL-1 or IL-6 (or both) driven condition.
    - Often responds better to blocking these cytokines than TNF-α
- Anakinra.
  - IL-1–receptor antagonist
  - Proven effective in children who have not responded adequately to TNF-α inhibitors
  - Should not be administered in combination with a TNF-α inhibitor or any other biological agent
- Canakinumab.
  - Monoclonal antibody also directed toward IL-1
  - Recently approved for treating systemic onset JIA
- Tocilizumab.
  - Provides IL-6 blockade
  - An addition to the treatment armamentarium
- Abatacept.
  - Recently approved for treating children with JIA
  - Selectively modulates the CD80/CD86:CD28 costimulatory signal required for full T-cell activation
  - Demonstrated efficacy in children and adults with arthritis who have not responded adequately to TNF-α inhibitors
- Rituximab.
  - Monoclonal antibody directed against the CD20 marker on B lymphocytes
  - Currently approved for adults not responding to TNF-α blockade
  - Not yet determined for use in children

Corticosteroids

- Monoclonal antibodies have rendered systemic corticosteroid use in JIA much less necessary.
- Corticosteroids remain important and effective medications, and use should follow these maxims.
  - They should be administered only when other agents have failed or when the child is seriously ill or has progressive severe chronic anterior uveitis unresponsive to local or other systemic therapy.
  - Administer as small a dose as possible.
  - Their use should be tapered and discontinued as soon as possible.
- Corticosteroids are effective anti-inflammatory agents but do not alter the course of the disease.
- Can be extremely difficult to discontinue in children with JIA.
- Long-term use is associated with many serious

adverse effects, including
- Immunosuppression
- Osteoporosis
- Growth retardation

- Small daily doses of prednisone may be effective in treating pain and stiffness.
- Higher doses may be needed to manage systemic features, such as pericarditis.
- High-dose IV pulse corticosteroid therapy can be useful in dire situations but is not more effective as chronic therapy.
- Intra-articular corticosteroids now play a larger role, especially in oligoarticular JIA.
  - Can be effective in controlling acute problems associated with one or several active joints
  - Usually used in combination with systemic, ongoing therapy
- Children with a painful or swollen joint frequently respond to arthrocentesis and instillation of a long-acting corticosteroid preparation (eg, triamcinolone hexacetonide).
  - This procedure should not be performed >3 or 4 times per year.
  - The physician should be absolutely certain that concomitant infectious arthritis is not the cause of the acute joint problem.
  - Early use of intra-articular corticosteroids may even have the potential to modify the course of JIA.

Stem Cell Therapy

- Despite this progress in treatments, there are still children whose disease has proven unresponsive to all of these and other interventions.
- In a select group, the use of autologous stem cell and other transplantation has, at times, proven to be extraordinarily helpful.
- The risks are great, but for those children, the benefits can be as well.

Pain Management

- Because children with arthritis can experience acute and chronic pain at various times regardless of treatment, this is an important area that needs to be considered and addressed.
- Before intervening, determine whether the pain is from
  - Joint inflammation
  - Joint damage or other mechanical factors
  - Periarticular structures
  - Other issues
- Not all pain requires intervention with medications; various physical or other techniques can also be effective.

Physical and Occupational Therapy

- Crucial adjuncts to
  - Maintain strength and range of motion.
  - Prevent contractures.
  - Allow the best possible quality of life.
- All patients should be given a home program of therapy that is reviewed and updated regularly.
- Heat therapy often helps minimize morning stiffness.
  - Warm baths or using a sleeping bag at night
- Swimming is an excellent exercise; affected children should be encouraged to swim and participate in as many other activities as possible.
- Normal play is a form of physical and occupational therapy.
- The orthopedist's contribution ranges from the application of splints to operative tendon releases and capsulotomies.
  - Some children may require joint resurfacing or joint replacement surgery.
  - The orthopedist's perspective is an important part of disease management.

WHEN TO ADMIT

- Children with systemic onset JIA who develop severe chest pain with shortness of breath (suggesting pericarditis with hemodynamic compromise) or a change in voice quality and difficulty breathing (suggesting cricoarytenoid arthritis)
- Children with chronic arthritis who are receiving corticosteroid therapy and develop signs of severe infection
- Children with chronic arthritis who are receiving NSAIDs and have acute anemia and melanotic stools
- Children with long-standing polyarticular arthritis complicated by multiple joint contractures and weakness and who require a period of inpatient rehabilitation (eg, physical and occupational therapy)

WHEN TO REFER

- Children with persistent oligoarticular or polyarticular joint inflammation
- Children with spiking fevers and rash but no obvious infectious cause
- Children with persistent joint pain, limp, or asymmetric use of an extremity for which no explanation has been found

FOLLOW-UP

- Risk of uveitis decreases with time and varies by JIA subtype and age at diagnosis.
  - Prescribed intervals between examinations vary, eventually lengthening after several years if no uveitis is present (**Table 1**).
  - Persistent oligoarticular JIA.
    - Regular ophthalmologic evaluation for uveitis, including slit-lamp examinations, should be
      - Instituted early
      - Performed every 4–6 months
      - Continued indefinitely
  - Children with extended oligoarthritis should be monitored closely, although uveitis is more common in children with the persistent type.

COMPLICATIONS

- Joint related
  - Pain
  - Loss of mobility
  - Impaired growth
  - Leg-length discrepancy
  - Muscle atrophy
  - Destructive arthropathy
- Uveitis
- Psychosocial effects
- Treatment side effects

PROGNOSIS

- JIA is rarely fatal, and, in general, the long-term prognosis is good.
- ~60%–75% of children will undergo remission at some point; many children will experience permanent remission.
- Most children with JIA will complete school, be gainfully employed, and raise families.
- Patterns of disease activity.
  - Persistent active arthritis and destructive arthropathy
  - Active disease, then remission
  - Polycyclic diseases characterized by acute flares of activity followed by temporary remissions
  - Low-grade continued disease activity with little, if any, joint destruction
- Oligoarticular JIA.
  - Children with oligoarticular arthritis and no chronic anterior uveitis have the best prognosis.
  - 40%–50% of children undergo complete remission.
  - Persistent oligoarthritis.
    - The course can be extremely variable.
    - Some children have a single episode; others may have recurrent exacerbation and remission.
    - This group has the fewest musculoskeletal complications and more long-term remissions.

Table 1. Frequency of Ophthalmologic Examination in Patients With Juvenile Rheumatoid Arthritis[a]

Type	ANA	Age at Onset (y)	Duration of Disease (y)	Risk Category	Eye Examination Frequency (mo)
Oligoarthritis or polyarthritis	+	≤6	≤4	High	3
	+	≤6	>4	Moderate	6
	+	≤6	>7	Low	12
	+	>6	≤4	Moderate	6
	+	>6	>4	Low	12
	–	≤6	≤4	Moderate	6
	–	≤6	>4	Low	12
	–	>6	NA	Low	12
Systemic disease (eg, fever, rash)	NA	NA	NA	Low	12

Abbreviations: ANA, antinuclear antibodies; NA, not applicable; +, positive; –, negative.

[a] Recommendations are to continue follow-up through childhood and adolescence.

From Cassidy J, Kivlin J, Lindsley C, Nocton J; American Academy of Pediatrics Section on Rheumatology and Section on Ophthalmology. Ophthalmologic examinations in children with juvenile rheumatoid arthritis. *Pediatrics*. 2006;117(5):1843–1845.

- Extended oligoarthritis.
  - Fewer children in this subgroup enter a prolonged remission than do those with persistent oligoarthritis, and they fare better than children with polyarthritis-onset disease.

- Systemic onset JIA.
  - 25%–30% undergo complete remission.
  - Younger children with systemic onset and polyarticular arthritis have a poorer articular prognosis.
  - Poor prognostic signs include
    - Continued presence of systemic features
    - Platelet count >600,000 cells/mm 6 months after onset
  - At least one-third of these children will develop severe arthritis.

- Polyarticular JIA.
  - 25%–30% undergo complete remission.
  - RF-negative polyarticular JIA.
    - Overall better prognosis than children with RF-positive polyarticular JIA.
    - Typically respond better to therapy and have a lower frequency of severe, early, crippling arthritis but may develop significant problems.

DEFINITION

- An acute, multisystem vasculitis of infancy and early childhood
- Characterized by
  - High fever
  - Rash
  - Conjunctivitis
  - Inflammation of the mucous membranes
  - Erythematous induration of the hands and feet
  - Cervical adenopathy
- Formerly known as *mucocutaneous lymph node syndrome*

SIGNS AND SYMPTOMS

Typical Kawasaki Disease

Criteria

- Fever of unknown cause lasting ≥5 days *and*
- At least 4 of the following 5 symptoms:
  - Bilateral congestion of ocular bulbar nonexudative conjunctivae with limbic sparing
  - Changes of lips (fissuring, redness) and oral cavity (erythema of mucosa, strawberry tongue)
  - Polymorphous rash without vesicles or crust
  - Unilateral nonsuppurative lymphadenopathy measuring >1.5 cm
  - Changes of the peripheral extremities (indurative edema, reddened palms and soles; late periungual desquamation)
- Other significant symptoms or findings
  - Carditis, especially myocarditis or pericarditis
  - Diarrhea
  - Arthralgia or arthritis
  - Proteinuria and increase of leukocytes in urine sediment
- Changes in blood tests
  - Leukocytosis with shift to the left
  - Slight decrease in erythrocyte and hemoglobin levels
  - Increased sedimentation rate
  - Elevated C-reactive protein (CRP)
  - Thrombocytosis in convalescent phase
- Changes occasionally observed
  - Aseptic meningitis
  - Mild jaundice or slight increase of serum transaminase

Phases

- The course of the disease can best be described as triphasic.
- Symptoms are not all apparent simultaneously, but the timing of their appearance is remarkably constant.
- Acute phase.
  - Fever
  - Oropharyngeal erythema
  - Swelling of hands and feet
  - Polymorphous erythematous rash
  - Cervical lymphadenopathy
- Subacute phase.
  - Begins after 10–12 days of the illness, when fever, rash, and lymphadenopathy fade
  - Characterized by
    - Lip cracking and fissuring
    - Unusual desquamation of the skin, beginning at the subungual and periungual regions of the fingers and toes
      - Occurs in nearly all cases 2–3 weeks after onset and after early signs involving the extremities have disappeared.
      - May progress to complete peeling of palms and soles, but exfoliation generally does not extend to remainder of body surface.
      - Onset of arthralgias or arthritis (or both), thrombocytosis, and cardiac disease
- Convalescent stage.
  - Usually begins ~25 days after onset
  - Characterized by
    - Absence of clinical signs of disease
    - Persistence of residual inflammation, marked by elevated erythrocyte sedimentation rate (ESR)

Symptoms

- Fever is the most prominent symptom of the acute phase.
  - High-spiking remittent pattern in the range of 38.4°C (101.1°F) to >40.0°C (104.0°F)
  - Persists despite use of empirical antibiotics, corticosteroids, and standard doses of antipyretics
  - Is present on average for ~12 days, although prolonged courses of ≤5 weeks have been reported; defervescence over 1–3 days
- Conjunctival hyperemia.
  - Discrete engorgement of the bulbar conjunctivae blood vessels (without associated discharge, exudate, keratitis, chemosis, or pseudomembrane formation) and anterior uveitis develop shortly after the onset of fever.
  - The cornea, lens, and retina are not involved.

- Early oropharyngeal signs include dryness and reddening of lips and of buccal and pharyngeal mucosa.
  - Absence of aphthous ulceration or hemorrhagic bullae is noticeable.
  - A strawberry tongue often is present.
  - Later, as intensity of the erythema subsides, lips usually become cracked and fissured.
- The most characteristic and unique feature of Kawasaki disease are changes in the hands and feet.
  - Early on, they become diffusely indurated and swollen; overlying skin develops a woody firmness suggestive of acute scleroderma.
  - Palms and soles usually become erythematous or purplish.
  - Fusiform swelling of the fingers, which limits the child's ability to grasp objects.
  - Feet are painful to the touch, and many children refuse to stand or walk.
  - During convalescent phase, deep transverse grooves (Beau lines) may appear across fingernails and toenails, presumably as a result of arrested growth during illness.
- A polymorphous, erythematous rash appears 1–5 days after the onset of fever.
  - Usually begins on the extremities and spreads centripetally.
  - The 3 most common patterns are
    - Maculopapular (morbilliform)
    - Erythema multiforme–like with iris lesions
    - Scarlatiniform
  - The rash may be coalescent, producing large, irregular, raised plaques, and may be pruritic.
  - Vesicles, pustules, and bullae are not seen.
  - The rash is not petechial or purpuric.
  - Rash usually fades within 1 week but occasionally persists longer or recurs.
- Lymphadenopathy.
  - Typically involves a single cervical node measuring >1.5 cm in diameter.
    - The node usually is not tender or warm and does not become fluctuant.
    - The lymph node diminishes in size with defervescence of the disease.
  - Generalized lymphadenopathy does not occur.
  - The least often seen of the major criteria.
    - Occurs in only ~60% of patients in most US series
- Sterile pyuria occurs more often than lymphadenopathy in most US cases.
  - 10–100 white blood cells (WBCs) per high-power field may be observed on a clean-catch voided urine specimen.
    - No WBCs will be seen on a bladder aspiration specimen because the sterile pyuria is caused by urethral inflammation or ulceration.
  - Occasionally, trace proteinuria or hematuria.
- Irritability, mild meningismus, and lethargy are seen in nearly all, and nearly all probably have aseptic meningitis.
- Cerebrospinal fluid (CSF) typically shows 25–100 WBCs/mm^3 with normal amounts of glucose and protein.
- Diarrhea is seen in ~50%.
  - Passing 5–15 stools per day for 2–7 days during the acute or subacute phase is common.
  - Stools do not contain polymorphonuclear cells and do not test positive for occult blood.
- Arthralgias, arthritis, or both occur in 30%–40%.
  - Large joints, particularly knees and ankles, are involved most often.
  - Usually, no more than 2 or 3 joints will be affected.
  - Joint symptoms occur 8–12 days after the onset of disease.
  - Joint fluid, if analyzed, reveals findings similar to those of rheumatoid arthritis.
- Pneumonia, tympanitis, photophobia, and mild liver dysfunction are somewhat less common.
- Acute hydrops of the gallbladder, jaundice, convulsions, encephalopathy, Bell palsy, hearing loss, pancreatitis, orchitis, and pleural effusions are seen rarely but are clearly associated features of Kawasaki disease.
- Cardiovascular system findings.
  - Disease mortality results from coronary artery aneurysm rupture or occlusion.
  - During the acute phase, tachycardia and gallop rhythms may appear.
  - However, the most serious manifestations of cardiac involvement occur during the subacute phase.
  - Manifestations may include
    - Serious arrhythmias
    - Congestive heart failure
    - Pericardial effusion
    - Mitral insufficiency
    - Myocardial ischemia or infarction

- Infants <6 months with Kawasaki disease.
  - High risk for coronary abnormalities
    - Highest risk (≥50%) for coronary artery lesions if untreated.
    - Manifestations are often subtle; fever, rash, and CSF pleocytosis may be misdiagnosed as viral meningitis.
    - Inflammatory markers are routinely elevated.
    - Echocardiography should be considered in any infant <6 months with fever for >7 days, laboratory evidence of systemic inflammation, and no other explanation for febrile illness.

Unusual Manifestations of Kawasaki Disease[1]

- Consider Kawasaki disease in infants and children with unexplained fever for >5 days and 2 or 3 of the principal diagnostic criteria.
- Young infants may have fever only.
- Laboratory results are similar to those of classic cases.
- A shock presentation may be seen and mimic bacterial sepsis.
- A lymph node first presentation may occur, often in boys, and may mimic bacterial lymphadenitis.
- Usually, more typical features of Kawasaki disease follow initial presentation, and laboratory features are consistent with Kawasaki disease.

DIFFERENTIAL DIAGNOSIS

- The clinical picture, after all major features have exhibited, is generally not difficult to differentiate from other mucocutaneous syndromes.
  - Diagnostic challenges may occur in very young patients or those with unusual or incomplete presentation.
  - In the first days of the illness, a whole spectrum of acute febrile diseases might be considered.
  - By 3–5 days after onset, certain clinical features may be singled out as compatible with other diagnoses (eg, strawberry tongue, suggestive of streptococcal infection).
- 2 conditions most commonly mimic Kawasaki disease: streptococcal and staphylococcal exfoliative toxin syndrome.
  - However, if all signs and symptoms are considered carefully, the diagnosis is readily apparent.
- The clinical features of Kawasaki disease and other mucocutaneous disorders are compared in **Table 1.**
- Other conditions that share some aspects of Kawasaki disease include
  - Rubella
  - Rubeola
  - Infectious mononucleosis
  - Other viral exanthems
  - Juvenile rheumatoid arthritis
  - Febrile drug reactions or Stevens-Johnson syndrome (eg, caused by anticonvulsants or trimethoprim with sulfamethoxazole)
- The similarities between fatal Kawasaki disease and fatal infantile polyarteritis nodosa are striking.
  - Pathologically, the 2 diseases cannot be distinguished.
  - The exact relationship between them is undetermined.

LABORATORY FINDINGS

- No pathognomonic laboratory findings.
- Laboratory abnormalities that are seen commonly can help establish the diagnosis.
  - In the acute phase, most patients exhibit elevated WBC count with associated left shift.
    - WBC counts of 15,000–20,000/mm^3 are common and may remain elevated for 1–3 weeks.
  - Other laboratory abnormalities commonly seen in the acute phase include
    - Elevated ESR (mean >55 mm/h).
    - Increased CRP and β_2-globulin.
    - Mild normochromic, normocytic anemia for age.
    - Sterile pyuria in 70%.
      - 10–100 WBCs per high-power field may be observed on a clean-catch voided urine specimen.
      - No WBCs will be seen on bladder aspiration specimen because sterile pyuria is caused by urethral inflammation or ulceration.
    - Trace proteinuria or hematuria may occur.
    - Elevated serum bilirubin, hypoalbuminemia, thrombocytopenia early on.
    - Hyponatremia.
    - Low albumin, anemia, and thrombocytopenia (poor prognostic factors).
    - CSF typically shows 25–100 WBCs/mm^3 with normal amounts of glucose and protein.
    - Slight decrease in erythrocyte and hemoglobin levels.
  - Many patients demonstrate sterile pyuria and CSF pleocytosis.

Table 1. Clinical Features of Kawasaki Disease and Other Mucocutaneous Diseases

	Kawasaki Disease	Stevens-Johnson Syndrome	Streptococcal Scarlet Fever	Staphylococcal Toxin Syndrome	Staphylococcal Toxic Shock Syndrome	Leptospirosis
Age (y)	Usually <5	Usually 3–30	Usually 5–10	Usually 2–8	Usually adolescent	Usually >2
Fever	Prolonged	Prolonged	Variable	Variable	Usually variable	–
Eyes	Hyperemia of ocular conjunctivae with limbic sparing; uveitis	Catarrhal conjunctivitis; chemosis; iritis; uveitis; panophthalmitis	No change	Hyperemia of ocular conjunctivae	Hyperemia of ocular conjunctivae	Suffusion of ocular conjunctivae; uveitis
Lips	Red, dry, fissured	Erosions; crusted, fissured, bleeding	No change	No change	Red	No change
Oral cavity	Diffuse erythema; strawberry tongue	Erythema; bullae, ulcers, pseudomembrane formation	Pharyngitis; palatal petechiae; strawberry tongue	Pharyngitis	Erythema; pharyngitis	Pharyngitis
Peripheral extremities	Erythema of palms and soles; indurative edema; periungual, palmar, and plantar desquamation after 2–3 wk	No change	–	No change	Swelling of hands and feet; dry gangrene, peripheral desquamation after 1–2 wk	Gangrene of hands and feet (rare)
Exanthem	Erythematous, polymorphous	Erythematous, polymorphous; iris lesions, vesicles, bullae, crusts	Finely popular erythroderma; Pastia lines; circumoral pallor, generalized rash may desquamate	Finely papular erythroderma; Pastia lines	Erythroderma	Erythematous, maculopapular, petechial, or purpuric

Table 1 (*continued*)

	Kawasaki Disease	Stevens-Johnson Syndrome	Streptococcal Scarlet Fever	Staphylococcal Toxin Syndrome	Staphylococcal Toxic Shock Syndrome	Leptospirosis
Cervical lymph nodes	Nonpurulent swelling, unilateral	Nonpurulent swelling (occasional)	Nonpurulent or purulent swelling (frequent)	Nonpurulent or purulent swelling (occasional)	No change	Nonpurulent swelling (infrequent)
Other	Meatitis; diarrhea; arthralgia and arthritis; aseptic meningitis	Malaise; cough, rhinorrhea, pneumonitis; vomiting; arthralgia; recurrent episodes	Malaise; vomiting; headache	–	Headache; confusion; hypotension; icteric hepatitis; diarrhea; coagulopathy; renal injury	Headache; myalgia; abdominal pain; icteric hepatitis; meningitis

- In weeks 2–3 of illness, patients characteristically develop significant thrombocytosis, with platelet counts averaging >700,000/mm^3.

- Importantly, results of several laboratory studies are negative.
  - Routine cultures of blood, CSF, urine, throat, and lymph node aspirates reveal no growth or normal flora.
  - Serologic studies for bacterial and viral agents are negative, including the antistreptolysin titer.
  - Antinuclear antibodies, rheumatoid factor, and other autoantibodies are absent.
- Detection of a common respiratory virus–like parainfluenza, influenza, rhinovirus, or human metapneumovirus does not exclude the diagnosis in a child who otherwise meets criteria for Kawasaki disease.
  - Diagnostic challenge may be posed in the child with fever and exudative pharyngitis related to adenovirus infection.
  - In such cases, if adenovirus is confirmed by detection in a nasopharyngeal swab, diagnosis of Kawasaki disease is considered unlikely.

IMAGING

- Echocardiography
  - Should be considered in any infant <6 months with
    - Fever for >7 days
    - Laboratory evidence of systemic inflammation
    - No other explanation for the febrile illness
  - Baseline echocardiogram should be performed as soon as the diagnosis of Kawasaki disease is suspected.
    - To evaluate cardiac function and the anatomy of the coronary arteries
      - Coronary artery abnormalities may develop as early as 5–7 days after illness onset but are generally apparent by the third or fourth week.
      - Coronary artery disease rarely, if ever, develops after 6–8 weeks, although late-onset valvular disease has been reported.
    - To assess for the presence or absence of pericardial effusion
    - To possibly reveal
      - Decreased left ventricular contractility
      - Mild valvular regurgitation (mitral regurgitation)
      - Pericardial effusion
    - In most cases the baseline echocardiogram is normal and does not exclude the diagnosis.

- Cases of atypical Kawasaki disease followed by typical coronary artery involvement have led to the suggestion that an echocardiography examination be performed in children with prolonged unexplained febrile illnesses associated with subsequent peripheral desquamation.
  - Although aneurysms rarely form before day 10 of the illness, perivascular brightness, ectasia, and lack of tapering of the coronary arteries can be seen in the acute stage.

DIAGNOSTIC PROCEDURES

- Electrocardiography
  - In the acute phase, may reveal
    - Sinus tachycardia
    - Nonspecific ST segment and T-wave changes
    - Evidence of mild left ventricular hypertrophy

TREATMENT APPROACH

- Treatment should begin as soon as diagnosis is established and as early as possible.
- Intravenous immunoglobulin (IVIG) with aspirin.
  - The best available therapy for preventing coronary artery abnormalities
  - Should be administered to all patients diagnosed within the first 10 days of the illness

SPECIFIC TREATMENTS

Aspirin

- Aspirin, given in high doses (80 mg/kg every 6 hours), reduces length and severity of Kawasaki disease during the acute phase.
  - Aspirin used early in the course of the disease may reduce coronary artery involvement.
  - Dosages should be reduced to 3–5 mg/kg/d after the child has been afebrile for 48–72 hours.
    - Thereafter, aspirin should be prescribed because of its antithrombotic effects at 3–5 mg/kg/d until platelet count has returned to normal.
  - If coronary aneurysms are recognized, salicylates (3–5 mg/kg/d) should be continued long term with careful cardiology follow-up and discontinuation with aneurysm resolution.

IVIG

- High-dose IVIG is effective for preventing coronary artery lesions in Kawasaki disease.
  - A single dose of 2 g/kg is infused over 10–12 hours.
  - No apparent difference exists in efficacy among particular IVIG products currently commercially available.
  - Patients should be monitored carefully during IVIG infusions for signs of anaphylaxis and immune hemolysis.
  - 80%–90% of children treated with IVIG respond favorably with decreased fever and reduction in mucocutaneous findings.
    - Remainder have persistent or recurrent fever, with or without mucocutaneous signs.
  - If ongoing fever cannot be attributed to another cause, the assumption should be made that Kawasaki disease is persisting or has relapsed.
    - Because fever may be viewed as a sign of continued vasculitis, retreatment with IVIG is advocated.
    - Most patients treated again after failure of a single dose of IVIG therapy will respond to retreatment.
    - Patients who remain symptomatic beyond the 10th day still may benefit from IVIG.
    - Decision to administer IVIG later than the 10th day must be individualized.
    - Timing of retreatment is important: IVIG retreatment is recommended if fever recurs or persists 36 hours after the end of first IVIG infusion.

Other Therapeutic Options

- Corticosteroids.
  - If IVIG therapy fails (particularly after 2 treatments), pulse-doses of methyl prednisolone at 30 mg/kg per dose for 1–3 days or infliximab as a single infusion should be administered.
    - This therapy should be reserved for patients who are clearly refractory to more established treatments (ie, failure of 2 doses of IVIG).
- Antibiotics are not indicated.
- It is important to counsel parents and pediatricians that live vaccines must be delayed for 11 months after IVIG and on the signs and symptoms of Reye syndrome while on aspirin therapy.

WHEN TO ADMIT

- All patients with Kawasaki disease should be admitted for treatment.

WHEN TO REFER

- Patients suspected of having atypical or incomplete Kawasaki disease
- Patients with Kawasaki disease who have not responded to 2 doses of IVIG
- Patients who have developed complications such as coronary dilatation and aneurysm

FOLLOW-UP

- For long-term management of patients with Kawasaki disease, a risk stratification scheme may be of benefit.
- Level I risk: no coronary artery abnormalities at any stage of the illness.
  - Primary care physician may fully assume care after the 1-year anniversary of disease onset.
  - Physical activities should not be restricted.
- Level II risk: transient coronary artery ectasia followed by regression.
  - A pediatric cardiologist should be consulted every 1–2 years.
  - ≥1 stress tests evaluating myocardial functioning should be performed at ~10 years of age.
- Level III risk: small to medium solitary coronary artery aneurysm.
  - Daily low-dose aspirin therapy
  - Annual cardiac follow-up with echocardiography and electrocardiography
  - Periodic stress tests recommended
- Level IV risk: ≥1 giant aneurysms or multiple aneurysms without obstruction.
  - Low-dose aspirin therapy should be maintained.
  - Low-dose warfarin should be considered.
  - Coronary angiography may be considered 6–12 months after acute disease has resolved, to delineate coronary artery anatomy.
  - Physical activities should be modified to minimize the risk of hemorrhage.
  - Strenuous or competitive sports should be avoided.
- Level V risk: coronary artery obstruction (thrombosis or stenosis).
  - Daily low-dose aspirin.
  - Warfarin should be considered.
  - Patients should be evaluated for indications for bypass graft surgery.
  - Mild to moderate recreational physical activities are permitted.

COMPLICATIONS

- Coronary artery aneurysm
  - Risk factors include
    - Missed or delayed diagnosis, including fever lasting >14 days
    - Boys
    - Extremes of age (<6 months, >9 years)
    - Asian, Pacific Islander, Hispanic children
    - Recurrent Kawasaki disease
  - If IVIG is not administered, aneurysms occur in 15%–25% of cases.
  - Usually apparent by echocardiogram during the subacute phase of the illness.
  - Coronary artery abnormalities can be seen in 2%–4% of cases, despite appropriate early therapy.
  - Most patients who have aneurysms are asymptomatic.
    - In some cases, formation of an aneurysm, particularly a giant aneurysm (>8 mm in diameter), is followed by thrombosis or rupture, resulting in a fatal myocardial infarction.
  - The care of a child with coronary involvement should always include consultation with a pediatric cardiologist experienced in management of Kawasaki disease.
  - Treatment of moderately large aneurysms may require anticoagulation with clopidogrel in combination with low-dose aspirin.
  - For those with giant aneurysms (or in young infants with an increase in coronary artery size >6 mm), anticoagulant therapy with warfarin or low-molecular-weight heparin is required.

PROGNOSIS

- Kawasaki disease is almost always self-limited and without complications, which should be emphasized to the parents.
  - Even if coronary artery aneurysms do develop, they resolve spontaneously in >50% of patients in 2 years and 80% in 5 years.
  - Long-term risks are undefined.
- Mortality rate is 0.2%.
- Death occurs almost exclusively in children who have giant aneurysms, largely as a result of coronary artery thrombosis, massive myocardial infarction, and cardiogenic shock.

- 80% of children whose aneurysms are small to moderate in size have complete resolution without apparent sequelae within 5 years.
- Those remaining may experience persisting aneurysms, coronary artery stenosis or obstruction, or aortic regurgitation.
  - Emerging evidence suggests that a portion of this group may be at risk for development of significant cardiovascular disease, such as coronary arteriosclerosis or persistent aneurysms, placing some at risk for sudden death from aneurysm rupture or thrombosis, cardiac arrhythmias, angina, or hypertension.

REFERENCE

1. From Newberger JW, Takahashi M, Gerber MA, et al. Diagnosis, treatment and long-term management of Kawasaki disease: a statement for health professionals from the Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease, Council on Cardiovascular Disease in the Young, American Heart Association. *Pediatrics.* 2004;114(6):1708–1733

Klinefelter Syndrome

DEFINITION

- Group of disorders characterized by the presence of ≥1 extra X chromosome in a male.
- ~80% of cases are caused by one extra X chromosome with karyotype 47,XXY.
- The typical patient with Klinefelter syndrome has
  - Long limbs
  - Narrow shoulders
  - Sparse hair
  - Small penis and testes
  - Azoospermia and gynecomastia
- Common characteristics include
  - Infertility
  - Difficulties in expressive language and reading
- Many patients with very subtle clinical features remain undiagnosed for several years.

SIGNS AND SYMPTOMS

- Typical presentations include
  - Toddlers
    - Usually present with developmental delay involving expressive language
  - School age
    - Most require assistance with reading and spelling.
    - Some might have behavioral and social problems.
  - Older age/puberty
    - Incomplete pubertal development
    - Gynecomastia
    - Small testes
  - Adulthood
    - Infertility and breast cancer
- Physical examination.
  - Longer arms and legs, with a low upper to lower segment ratio.
  - Low biacromial diameter, probably due to low testosterone levels.
  - Height.
    - Range: 25th–99th percentile for age
    - Mean: 75th percentile
    - Most height gain takes place between ages 5 and 8 years.
  - Head circumference and weight: usually at the 50th percentile.
  - Testicular volume and penile length.
    - In childhood: slightly lower than normal
    - During adolescence: small testicular size (<2.5 cm) and average volume (<4 mL)
  - Many individuals enter puberty normally, but testosterone levels tend to decrease in late adolescence to adulthood.
  - Insufficient androgens present.
    - Usually less than half the level seen in unaffected individuals
  - Secondary sexual characteristics do not completely develop.
    - Inadequate virilization
    - Sparse body and facial hair
    - Gynecomastia in more than half of adolescent patients
  - Most common minor anomaly.
    - Fifth finger clinodactyly in almost one-third of patients
  - Other anomalies include
    - Cleft palate
    - Cryptorchidism
    - Inguinal hernia
    - Scoliosis
    - Increased frequency of chronic bronchitis and diabetes mellitus
    - Severe acne
    - Hypospadias
- Most patients are infertile, with hyalinization and fibrosis of the seminiferous tubules by mid-puberty.
  - Although only a minority of patients have viable sperm in the ejaculate, recent advances in reproductive technology have increased their reproductive potential.
    - Testicular sperm extraction
    - Intracytoplasmic sperm injection
- Psychological performance.
  - Significant psychiatric problems are uncommon.
  - IQ scores.
    - The number of extra X chromosomes adversely affects the final intellectual performance.
    - IQ scores vary widely, from well below to well above average.
      - Mean IQ score: 85–90
      - Each extra chromosome decreases the IQ score by 15–16 points.
      - Verbal IQ score is usually lower than performance IQ score, most likely secondary to auditory processing and expressive language difficulties.
  - Effects on auditory memory cause reading and spelling problems.
  - Expressive language is more severely affected than receptive skills and comprehension.

- Individuals with 47,XXY karyotype tend to present with
  - — Shyness
  - — Immaturity
  - — Social insecurity
  - — Problems in the formation of peer relationships
  - — Increased anxiety and substance abuse

DIFFERENTIAL DIAGNOSIS

- Other causes of hypogonadism, such as Kallmann syndrome.
- Other causes of infertility in males.
- Marfan syndrome.
- Fragile X syndrome.
- *SRY* gene translocations to the X chromosome have a 46,XX karyotype.

DIAGNOSTIC APPROACH

- Clinical presentation of Klinefelter syndrome can vary.
- High index of clinical suspicion is necessary to reach a diagnosis in most patients.
- Diagnosis at birth is difficult to make because most patients do not have specific phenotypic characteristics or distinct facial dysmorphic features.

LABORATORY FINDINGS

- Prenatal chromosome analysis.
  - Amniocentesis (14–16 weeks)
  - Chorionic villus sampling (11–12 weeks)
- If the diagnosis is not made prenatally, chromosome analysis from peripheral blood lymphocytes can be performed based on clinical examination findings.
- Barr-body analysis.
  - Sensitivity ≤82%
  - Not widely used today
- Androgen receptor gene quantitative real-time polymerase chain reaction.
  - Detects the number of *AR* genes and, thus, the number of X chromosomes
- Karyotype analysis.
  - Gold standard
  - Reveals ≥2 X chromosomes in addition to a Y chromosome in a phenotypical male
- Chromosomal microarray analysis.
  - Detects duplication of X chromosomal material
- A complete hormonal evaluation includes
  - Follicle-stimulating hormone (FSH) elevated
  - Luteinizing hormone (LH) elevated
  - Testosterone low to low-normal when patient is not on testosterone therapy
  - Estradiol elevated
  - Insulinlike growth factor 1
  - Prolactin
- Inhibin B decreases to undetectable levels after puberty.
- Measure cortisol levels because of increased frequency of adrenal steroidogenic deficiency in Klinefelter syndrome.
- Decreased serum osteocalcin levels and increased hydroxyproline to creatinine ratio show decreased bone formation and increased bone resorption.
- Despite increased risk of deep venous thrombosis and pulmonary embolism, it is not clear whether routine testing for thrombophilia is indicated.

IMAGING

- Routine bone density screening to test for osteopenia or osteoporosis
- Echocardiography to assess for mitral valve prolapse
- Radiography to evaluate for radioulnar synostosis and taurodontism (vertical enlargement of the body of the tooth affecting molar teeth)

DIAGNOSTIC PROCEDURES

- Histology.
- Testicular biopsies of prepubertal patients reveal reduced numbers of germ cells with normal numbers of Sertoli and Leydig cells.
- Later in adulthood, hyalinization of seminiferous tubules with fibrosis and rare, if any, foci of spermatogenesis are seen.
- Gynecomastia breasts reveal hyperplasia of interductal tissue.

TREATMENT APPROACH

- Treatment should be based on a multidisciplinary approach by
  - Pediatricians
  - Geneticists
  - Endocrinologists
  - Infertility specialists
  - Speech therapists
- Management strategies depend on age at diagnosis.

SPECIFIC TREATMENTS

- Testosterone.
  - Start as early as possible (by around age 12 years [onset of puberty] when gonadotrophin levels begin to increase).
  - Begin treatment even if testosterone levels are in the low-normal range.
  - Necessary for an increase in muscle bulk and bone mineral density.
  - Treat all patients with increased gonadotrophin levels and those with symptoms of hypogonadism (eg, decreased libido, fatigue).
  - Aim is to achieve a testosterone level in the middle of the normal range.
  - Careful adjustment of dose can normalize serum testosterone, estradiol, FSH, and LH.
  - Testosterone will not treat infertility, gynecomastia, and small testicular size.
  - Other benefits include
    - Proper development of secondary sexual characteristics
    - Increases in energy and concentration
    - Fewer problems with social interactions
  - Continue for life to reduce osteoporosis, autoimmune disease, diabetes mellitus, and obesity.
  - Potential complications include
    - Weight gain secondary to increased lean body mass and fluid accumulation
    - Acne
    - Low levels of high-density lipoprotein (HDL)
    - Erythrocytosis
  - Treat micropenis with topical testosterone in the form of a cream or testosterone injections.
- Treat gynecomastia with mastectomy.

WHEN TO REFER

- Support from a clinical psychologist or psychiatrist is often necessary.
- Speech therapist for speech delay in early childhood.
- Monitor school performance with appropriate specialist referrals for other learning problems as needed.
- Physical and occupational therapy as needed for
  - Hypotonia
  - Motor skill delay
  - Balance and coordination impairment
  - Dyspraxia

COMPLICATIONS

- Breast carcinoma and other tumors
  - Risk for breast carcinoma in patients with 47,XXY is several times higher than that of karyotypically normal males of same age.
  - Increased surveillance for breast cancer during routine annual physical examination seems reasonable, but more studies are needed.
  - Association with mediastinal germ-cell tumors has been reported.
  - Mortality from lung cancer and incidence of non-Hodgkin lymphoma seem to be elevated.
- Autoimmune diseases
  - Rheumatoid arthritis.
  - Systemic lupus erythematosus.
  - Sjögren syndrome.
  - Risk considered to be similar to that seen in females.
- Endocrine complications
  - Metabolic syndrome
  - Increased risk for diabetes mellitus
  - Increased levels of low-density lipoprotein cholesterol and decreased levels of HDL cholesterol
  - Higher fasting plasma insulin levels and insulin resistance
  - Hypothyroidism and hypoparathyroidism
- Varicosities
  - Venous stasis resulting in varicose veins and venous ulcers
  - Venous leg ulcers 20–50× higher than in the general population
- Osteoporosis
  - 25%–40% of patients have decreased bone density compared with controls.
  - Increased morbidity and mortality.
    - Increased rates of admission for hip, forearm, and spine fractures
    - Increased risk of death from hip fractures
- Cardiovascular disease
  - Increased mortality from cardiovascular disease related to higher incidence of
    - Mitral valve prolapse and increased risk of sudden death
    - Leg ulcers associated with increased risk of deep venous thrombosis and pulmonary embolism

PROGNOSIS

- Overall prognosis is good and life span is normal.
- Final prognosis depends on occurrence of complications.
- Males with 47,XXY karyotype may have difficulties through adolescence and encounter academic, behavioral, and psychiatric problems.
- Most become independent from their families in later life and achieve normal functional levels.

PREVENTION

- Karyotypic analysis is not routinely performed in parents of patients with Klinefelter syndrome.
- The recurrence risk is thought to be <1%.
- There is an increased risk of aneuploidy and a higher frequency of trisomy in offspring.
- Preimplantation genetic diagnosis and prenatal diagnosis should be offered.

Labial Adhesions

DEFINITION

- Labial adhesions are membranous structures that develop as a result of fusion of the adjacent mucosal surfaces of the labia minora.
- Also known as *labial agglutination* or *synechia vulvae.*

SIGNS AND SYMPTOMS

- Labial adhesions often are asymptomatic.
  - Discovered at routine well-child visits
  - Brought to the attention of the pediatrician by the child's caregiver
- If the adhesions partially dehisce, the child may experience
  - Spotting of a minute amount of blood
  - Irritation
- Uncommon symptoms include
  - Pain with urination
  - Vaginal pain
  - Pain with ambulation
  - Urinary retention
  - Altered urinary stream
  - Other symptoms suggestive of urinary tract infection (UTI)
  - History of recurrent UTI
- The membranous structure can vary from thin and transparent to thick and fibrous.
- Any degree of labial involvement can occur, including covering of the urethral meatus.

DIFFERENTIAL DIAGNOSIS

- Conditions that may be confused with labial adhesions include
  - Ambiguous genitalia
  - Vaginal agenesis
  - Imperforate hymen
  - Septated hymen
- Physical examination easily differentiates these entities.
  - A line of demarcation between the clitoral hood and labia minora is
    - Present with labial adhesions
    - Not present with ambiguous genitalia secondary to androgen excess
  - In vaginal agenesis and hymenal variants, the labia are normal and unfused.
    - The characteristic findings of these entities are located in the vaginal introitus.

DIAGNOSTIC APPROACH

- The condition is diagnosed by visual inspection of the vulva.
  - Includes hymenal examination in the supine frog-leg or prone knee-chest position
- The labia majora should be gently stretched apart.
  - A membrane of variable length and thickness is seen in the midline.
  - A small opening near the clitoris allows the outflow of urine.
- A line of adhesion between the 2 non-rugated labia minora or raphae also may be seen.

LABORATORY FINDINGS

- Urinalysis and urine culture if the child has accompanying symptoms, such as
  - Pain on urination or ambulation
  - Altered urinary stream
  - Urinary retention
  - History of UTIs

TREATMENT APPROACH

- If the child has no accompanying symptoms, labial adhesions should not be treated.
- Any documented UTI or vulvar infection should be treated accordingly.

SPECIFIC TREATMENTS

Uncomplicated

- If the child has no accompanying symptoms, labial adhesions should not be treated.
- Parents should be given an opportunity to visualize the adhesion so they are not surprised and concerned about the unusual appearance of the vulva.
- Reassurance of the benign, self-limited nature of this condition and education about potential symptoms should be provided.

Complicated

- The first-line treatment of the complicated labial adhesion is topical estrogen.
  - Goal: to use the least amount of medication that will achieve separation of the adhesion.
  - 0.625 mg conjugated estrogen cream (Premarin Vaginal Cream, Pfizer).
    - Applied to the adhesion and labial edges with a fingertip or cotton swab.
    - Gentle traction should be placed on the opposing labia during the application.

  - Specific optimal dosing and length of treatment are unknown; twice-daily application for 2 weeks is a reasonable starting point.
  - Treatment produces thinning of the line of fusion.
    - Facilitates manual labial separation in the office
- Highly effective for most thin, transparent adhesions.
- Less effective in dense and fibrous or long-standing adhesions.
- Even dense adhesions should be treated initially with topical estrogens.
- Possible adverse effects of topical estrogen include
  - Breast budding and tenderness.
  - Vulvar hyperpigmentation.
  - Local irritation.
  - All these effects are reversible on discontinuation of the medication.
- After labia are separated
  - Topical lubricant (eg, white petroleum jelly) applied daily for several months
  - To ensure complete healing and persistent separation
- Treatment with estrogen cream is considered unsuccessful if
  - Labial separation has not occurred within 8 weeks.
  - The child suffers untoward effects from the estrogen and cannot continue using it.

- Retrospective reviews of girls treated with topical betamethasone have shown similar efficacy to topical estrogen.
- Manual separation if estrogen therapy is unsuccessful.
  - Topical anesthetic is applied to the affected area.
  - Firm traction on the opposing edges of the labia minora is applied to separate the fused edges.
  - Edges should be smoothly peeled away from each other.
  - After separation, a lubricant should be applied to the affected area daily for several months to prevent re-adherence.
  - Warm soaks or sitz baths in the days following separation may provide relief if the vulva is irritated.
- Surgical treatment is rarely required.
  - Surgical lysis by a pediatric urologist or gynecologist while under general anesthesia
  - For thick labial adhesions that cannot be separated by the previously described treatments or adhesions associated with complications
  - The decision to treat labial adhesions with surgery is made by weighing
    - Significance and severity of symptoms after less aggressive treatments
    - Risks of general anesthesia
  - Postoperative care includes
    - Sitz baths in the immediate postoperative period
    - Application of topical lubricant for several months

WHEN TO REFER

- A symptomatic child with persistent or recurrent labial adhesions should be referred to a pediatric urologist or gynecologist for surgical lysis if she has
  - A history of UTIs
  - Urinary retention
  - Altered urinary stream
  - Dysuria
  - Pain with ambulation
  - Failed topical estrogen therapy

PROGNOSIS

- The condition is self-limiting.
- Spontaneous resolution in affected individuals has been reported to occur in
  - 50% of cases within 6 months
  - 90% of cases within 12 months
  - 100% of cases within 18 months

PREVENTION

- Explain the value of proper hygiene of the vulva.
- Educate the parents about practices to help their child avoid recurrent labial adhesions.
  - Wiping front to back after urination or defecation
  - Wearing cotton underwear
  - Avoiding application of detergents in the genital area
  - Avoiding wet, tight clothing against the vulva for prolonged periods

DEFINITION

- Learning difficulties occur at any age for a variety of reasons.
- They invariably cause frustration that can lead to or compound behavior problems and emotional distress.
- The effects can be profound, with economic and emotional consequences in adulthood.

HISTORY

- At routine health visits
  - Elicit parental concerns.
  - Monitor developmental progress and functioning.
  - Screen for developmental delays and symptoms of social and emotional problems.
  - Refer to reports from child care or school personnel.
  - Note a family history of learning problems.
- Symptoms and clinical findings suggesting learning difficulties include
  - Indications from youth's or parent's history
    - Delay in language development.
    - Difficulty understanding language despite normal hearing and vision.
    - Difficulty following directions.
    - Difficulty learning letters, numbers, and colors.
    - Struggling to read, grasp math concepts, or write in comparison with peers.
    - Letter reversals (b/d), inversions (m/w), transpositions (felt/left), substitutions (house/home), or confusion of arithmetic signs.
    - Avoids reading aloud, writing, or homework.
    - Frustration with academic performance.
    - Parent perceives child is "lazy," an underachiever.
    - Classroom behavior or inattention has become a problem.
    - Other family members experienced learning difficulties or did not complete high school.
  - Other measurements
    - End-of-grade test scores or achievement test scores.
      - Percentiles are low (≤15%) or markedly scattered.
      - Performance is considerably lower than expected for child's intelligence.
    - Grades are low or markedly scattered.
    - Intelligence tests are within normal range or significantly higher than measures of academic achievement.
- Adolescents
  - Who have been progressing normally with academics may suddenly develop learning difficulties
  - May have a mild learning disability (LD) for which he or she has compensated in lower grades
  - May have mild attentional problems that previously have not required intervention
  - Other causes or contributing factors
    - Inadequate sleep
    - Poor nutrition
    - Inadequate physical activity
    - Anxiety
    - Depression
    - Substance abuse
    - Issues of sexual orientation or bullying
- Differentiate symptoms from normal behavior.
  - Children learn at different rates.
    - Typically developing children ≤7 years may reverse and transpose letters and experience some frustration with new learning tasks.
    - Many children will have one or more of the previously noted symptoms from time to time.
  - Children who have missed school for an illness, changed schools, or experienced a significant loss may experience transient problems with school functioning.
  - Some parents have unrealistic expectations based on their own learning experiences or that of older siblings or children of friends.
  - Explore sources of stress in the family, school, or community as cause of inattentiveness and distraction in the child.
- Communicate with school personnel to request data and observations such as
  - Intelligence testing, cognitive screening, or psychological tests.
  - Achievement testing or reports.
  - Full psychoeducational evaluation.
  - School placement and special services.
  - Individualized education program (IEP) or 504 plan, if in place.
  - History of academic progress, behavior and discipline, and peer interactions.
  - Use additional instruments to identify children who may have contributing psychosocial problems.
    - NICHQ Vanderbilt Attention-Deficit/Hyperactivity Disorder (ADHD) Rating Scales
    - Pediatric Symptom Checklist (PSC)-35
    - PSC-17
    - Strengths and Difficulties Questionnaire (SDQ)

PHYSICAL EXAMINATION

- Preterm birth.
  - Higher risk for neurodevelopmental sequelae
    - Birth at <32 weeks' gestation
    - Perinatal and postnatal complications
    - Prolonged ventilation
    - Intracranial hemorrhage
    - Sepsis
    - Seizures
    - Prolonged acidosis
    - Hypoglycemia
- Congenital cardiac anomalies pose high risk for LDs.
- Genetic disorders linked to risk for LDs.
  - Klinefelter syndrome.
  - Turner syndrome.
  - Velocardiofacial syndrome.
  - Spina bifida with shunted hydrocephalus.
  - When one of these risk factors is identified, the physician should consider referral for psychological and educational assessment.

DIFFERENTIAL DIAGNOSIS

- Conditions that may cause poor school performance or co-occur with learning difficulties
  - Hearing or vision problems
  - Sleep deprivation
    - Inattention and irritability can contribute to poor school performance.
    - Poor school performance and homework struggles may contribute to difficulty sleeping.
  - Developmental problems
    - Overall intellectual or social limitations.
    - Children with low achievement and low intellectual levels often have the same problems as children with LDs.
  - ADHD
    - Children experiencing academic difficulties may seem restless and inattentive.
  - Exposure to adverse childhood experiences
    - Events posing high risk for emotional difficulties, such as adjustment disorder or post-traumatic stress disorder (PTSD).
      - Trauma
      - Violence
      - Natural disaster
      - Separation from a parent
      - Parental divorce or separation
      - Parental substance use
      - Neglect
      - Physical, emotional, or sexual abuse
    - Three hallmark symptom clusters of PTSD.
      - Reexperiencing
      - Avoidance of memories or situations that recall the trauma
      - Hypervigilance
    - Parents are often unaware of exposures that children may have had at school or in the community.
    - Major traumas in the family may not be discussed or disclosed (eg, serious illness in a parent, maltreatment of the child, death or incarceration of a loved one).
  - Anxiety
  - Bereavement
    - Death of a family member or friend.
    - Other losses may trigger grief responses.
      - Separation or divorce of parents
      - Relocation
      - Change of school
      - Deployment of a parent in military service
      - Breakup with a girlfriend or boyfriend
      - Remarriage of parent
  - Depression
    - May cause a decline in school performance
    - May result from poor school performance
    - May coexist with LDs
    - Indicators of depression
      - Marked sleep disturbance
      - Disturbed appetite
      - Low mood
      - Tearfulness
  - Physical illness
    - All illnesses that may interfere with the child's attendance.
    - Some illnesses (or symptoms) can affect attention.
      - Hypothyroidism or hyperthyroidism
      - Neurologic disorders
      - Post-traumatic brain injury
      - Undiagnosed diabetes
    - Side effects of medications.
      - Bronchodilators
      - Anticonvulsants
  - Substance use
    - Alleviation of frustration with school performance through substance use (alcohol, nicotine, or other drugs) or self-medication with caffeine or cocaine.
    - Children using substances may manifest inattention, impulsivity, and deteriorating school performance.

- Conduct or oppositional disorders
  - Frustration with poor academic performance can exacerbate conduct or oppositional problems.
- Autism spectrum disorder
  - Problems with social relatedness
    - Poor eye contact
    - Preference for solitary activities
    - Language (often stilted)
    - Range of interests (persistent and intense interest in a particular activity or subject)
    - Rigid expectations for routine

TREATMENT APPROACH

- The care of a child experiencing learning difficulties can begin in the primary care setting, even if problems do not rise to the level of a disorder or referral.
- The primary care physician may be responsible for
  - Advising the family about the child's rights under the Individuals With Disabilities Education Act (IDEA)
  - Reducing stresses on the child while awaiting further assessment and treatment
  - Engaging and encouraging the child's positive view of his or her evaluation and specialized instruction
  - Monitoring academic progress
  - Observing for and addressing any comorbidities
  - Coordinating care provided by parents, school, medical home, and specialists
  - Reviewing with the family whether school interventions are evidence based, or referring to a developmental-behavioral pediatrician

SPECIFIC TREATMENT

- Engage child and family in care.
  - The process may require multiple primary care visits.
  - Reinforce strengths of the child and family.
  - Identify barriers to addressing the problem.
  - Use "common factors" techniques to build a therapeutic alliance with the child and family (**Box 1**).
  - The primary care physician can encourage a positive view of treatment on the part of the child and family.
- Encourage healthy habits.
  - Exercise.
  - Outdoor play.
  - Balanced and consistent diet.
  - Sleep.
  - Avoidance of exposure to frightening or violent media.
  - Limitation of screen time to <1–2 hours per day.
  - Special time with parents.
  - Acknowledgment of child's strengths.
  - Help child feel competent, special, positive, and appreciated.
- Reduce stress.
  - Consider the child's social environment.
    - Family social history
    - Parental depression screening
    - Results of family assessment tools
    - Reports from child care or school
  - Is the parent punitive or critical?
    - If parents' psychosocial problems affect relationship with the child, explore readiness to address them.
    - Encourage praise for the child's efforts.
    - Avoid comparisons with siblings or peers.
    - Nurture the child's nonacademic gifts, such as art or music.
    - Encourage participation in extracurricular activities (eg, scouts, faith-based youth group, boys' or girls' club).
  - Are there battles over homework?
    - Advise parents that the child is not lazy.
    - Guidelines for homework.
      - Establish a routine (eg, not waiting until evening to get started).
      - Identify another student who the child can call to clarify homework assignments.
      - Limit distractions (eg, TV, computer, phone).
      - Help divide assignments into small, manageable segments (especially long-range assignments and projects).
      - Help child get started (eg, read directions together, watch child complete first items).
      - Monitor without taking over.
      - Praise good effort and completion of tasks.
      - Do not insist on perfection.
      - Offer incentives ("When you've finished, we can...").
      - Help child study for tests.
      - Do not force excessive time on homework.
      - Write a note to the teacher if the child put forth good effort but was not able to complete assignment.
      - If child fails to turn in completed work, develop a system with the teacher to collect it on arrival.

Box 1. HELP Build a Therapeutic Alliance

H = Hope

Increase the family's hopefulness by describing your realistic expectations for improvement and reinforcing the strengths and assets you see in the child and family.

E = Empathy

Communicate empathy by listening attentively.

L^2 = Language, Loyalty

Use the child's or family's own language to reflect your understanding of the problem as they see it and to give the child and family an opportunity to correct any misperceptions.

Communicate loyalty to the family by expressing your support and your commitment to help.

P^3 = Permission, Partnership, Plan

Ask the family's permission for you to ask more in-depth questions or make suggestions for further evaluation or management.

Partner with the child and family to identify any barriers or resistance to addressing the problem, find strategies to bypass or overcome barriers, and find agreement on achievable steps aligned with the family's motivation.

Establish a plan (or incremental first step) through which the child and family will take some action(s), work toward greater readiness to take action, or monitor the problem, and then follow up with you, based on the child and family's preferences and sense of urgency. (The plan might include, for example, gathering information from other sources such as the child's school, making lifestyle changes, applying parenting strategies or self-management techniques, reviewing educational resources about the problem or condition, initiating specific treatment, seeking referral for further assessment or treatment, or returning for further family discussion.)

From American Academy of Pediatrics. *Addressing Mental Health Concerns in Primary Care: A Clinician's Toolkit* [CD-ROM]. Elk Grove Village, IL: American Academy of Pediatrics; 2010.

    - If unable to provide supervision and assistance, or if homework battles are adversely affecting parent-child relationship, ask the teacher for help finding a tutor.
- Is the child exposed to criticism or teasing at school? Is the child's teacher supportive and patient?
  - Provide strategies for communication between school personnel and home.
  - Praise progress and effort, not just outcomes.
  - Address teasing or bullying.
- Are school authorities proceeding with assessment in accordance with the child's rights?
  - Inform parents about the child's rights under IDEA and Section 504 of the Rehabilitation Act.
  - Children with an LD qualify for specialized educational services.
  - IDEA requires that the school develop an IEP that
    - Documents the child's current level of functioning
    - Establishes goals
    - Delineates services needed to meet those goals in the least restrictive environment possible
  - The parent is entitled to meet with school personnel to review and approve the IEP.
  - If the child does not qualify for specialized educational services, identify minor challenges that can be helped by classroom modifications, or a 504 plan.
  - Parents dissatisfied with the school's response to the child's needs can appeal within the school system.
  - If the school is not adequately addressing the child's needs, the physician may offer referral to a community mental health professional.
    - Results of this assessment may support advocacy efforts in the school system or guide tutorial assistance.

  - Acknowledge and reinforce protective factors.
    - Good relationships with at least one parent or important adult
    - Pro-social peers
    - Concerned or caring family
    - Help-seeking behaviors
    - Connection to positive organization(s)
- Address comorbid conditions.
- Provide resources.
  - National Center for Learning Disabilities (www.ncld.org)
  - Wrightslaw for questions about special education law (www.wrightslaw.com)

WHEN TO REFER

- Involve education or mental health specialist(s) if child does not respond to initial interventions or if indicated by
  - The child or parent is very distressed by symptom(s).
  - Co-occurring behavior problems are not responsive to primary care management.
  - Incomplete or untimely school evaluation.
  - Parent's relationship with school is adversarial.
  - Child and family have conflicts that are not responsive to primary care management.
  - Parent is very negative toward child or unresponsive to primary care guidance.
- Consider a geneticist for a diagnostic workup if there are persistent concerns.

FOLLOW-UP

- School reports can be helpful in monitoring progress.
- Screening instruments that gather information from multiple reporters (youth, parent, teacher), such as the SDQ and PSC, can be helpful in monitoring progress with symptoms and functioning.

COMPLICATIONS

- Children who do not receive timely intervention are at risk not only for academic failure, but also for the psychosocial morbidities that accompany limited academic achievement, such as substance abuse and juvenile delinquency.

DEFINITION

- Learning disorders (LDs): learning challenges that significantly impede the ability to perform at the expected level in academics
- Individuals With Disabilities Education Act (IDEA) of 2004
  - Specifies regulations pertaining to public education services for persons with disabilities
  - Defines LD as
    - Disorder in one or more basic psychological processes involved in understanding or in using language, spoken or written.
    - Possibly manifest in imperfect ability to listen, think, speak, read, write, spell, or do mathematical calculations.
      - Includes conditions such as perceptual disabilities, brain injury, minimal brain dysfunction, dyslexia, and developmental aphasia
    - Does not include learning problems caused by visual, hearing, or motor disabilities; mental retardation (intellectual disability); emotional disturbance; or environmental, cultural, or economic disadvantage.
- *Diagnostic and Statistical Manual of Mental Disorders,* 5th Edition (*DSM-5*)
  - Defines *specific LD* as difficulties learning and using academic skills.
  - Subtypes include impairment in reading, written expression, and mathematics, which are further specified by severity level.
  - Learning difficulties begin during school-age years but may become fully evident only as academic demands increase.
  - Dyslexia and dyscalculia are alternative terms for impairment in reading and mathematics, respectively.
  - Dyslexia refers to specific reading disability, but educators prefer the term *learning disability.*

SIGNS AND SYMPTOMS

- LD occurs on a continuum of severity.
  - Most affected individuals experience mild to moderate impairment.
- LDs are heterogeneous, and it is not uncommon for an individual to have >1.
- Presenting symptoms vary according to age and the developmental demands.
- The major presenting complaint that should raise concern about possible LD is in a child who shows normal capabilities in most developmental areas and significant discrepancies in a set of specific skills.
  - Other presenting symptoms may include conflict between child and parent (eg, homework battles), parent's perception of child as lazy or defiant, and behavior problems or inattention in school.
- Core symptoms of reading, mathematics, and written expression disorders are shown in **Tables 1, 2,** and **3.**

DIFFERENTIAL DIAGNOSIS

- Primary differential diagnoses.
  - Attention-deficit/hyperactivity disorder (ADHD)
  - Generalized intellectual impairment
- Frequent comorbidity of these conditions (especially LD and ADHD) complicates diagnosis.
  - Comprehensive evaluation by an appropriately trained examiner is critical.
- For the growing number of American children whose first language is not English, academic difficulties may or may not have an LD component.
  - A thorough evaluation that includes an examiner with expertise in bilingual learning issues is essential in developing an appropriate education plan.

DIAGNOSTIC APPROACH

- Pursue diagnosis as early as possible.
  - Reading proficiency by the end of third grade is necessary for a high probability of future academic success.
  - The prime window of opportunity for effective targeted intervention is from preschool through third grade.
- Formal LD diagnosis typically does not occur until a child is ≥6 years because a persistent impairment in an academic skill is a major characteristic.
  - Earlier diagnosis should be considered tentative.
  - Frequent reevaluation is needed to determine whether cognitive pattern of concern persists.
- LD diagnosis is based on
  - Clinical and academic history
  - Standardized cognitive, language, academic, behavioral, and emotional measures
  - Formal psychological evaluation (required for a firm diagnosis)

Table 1. Signs and Symptoms of Reading Disability (Dyslexia)

Grade	Difficulty With
Prekindergarten–grade 1	Letters vs pictures or numbers
	Letter names and letter sounds
	Simple, high-frequency words (eg, *cat, boy, who*)
	Rhyming
	Separating and blending sounds within words
	Phonics
Grades 2–5	Phonics
	Automatic word recognition
	Reading aloud
	Spelling
	Sounding out longer words
	Longer reading and writing assignments
	Reading speed
	Reading comprehension
Grades ≥6	Skills tested for grades 2–5
	Written expression skills
	Learning a foreign language

Table 2. Signs and Symptoms of Mathematics Disability

Grade	Difficulty With
Prekindergarten–grade 1	Names of written numerals
	1-to-1 correspondence
	Rapid recognition of set size (eg, set of 3, set of 5)
	Concepts of more, less, and equal to
	Concepts of addition and subtraction
	Meanings of math symbols
	Memorizing simple addition and subtraction facts, 0–9
Grades 2–5	Memorizing addition and subtraction facts, 0–20
	Concept of place value
	Addition and subtraction with regrouping
	Relationships among numbers and strategic counting (eg, 2s, 5s, 10s)
	Word problems
	Concepts of time, money, and measurement
	Concepts of fractions and decimals

Table 2 (*continued*)

Grade	Difficulty With
Grades 2–5 (*continued*)	Concepts of multiplication and division
	Memorizing multiplication and division tables
Grades ≥6	Skills listed for grades 2–5
	Interpreting and creating charts and graphs
	Complex word problems
	Abstract geometric and algebraic concepts
	Math applications for personal finance (eg, calculating sales tax, interest rates)

Table 3. Signs and Symptoms of Written Expression Disability

Grade	Difficulty With
Prekindergarten–grade 1	Writing own name
	Writing all alphabet letters
	Copying
	Spatial aspects of writing (eg, writing on the line, spacing between letters and words)
	Spelling of simple sight vocabulary and words that follow basic phonics or orthographic patterns
Grades 2–5	Handwriting and copying
	Written grammar
	Spelling
	Basic aspects of written composition (eg, introductory or concluding sentences, logical sequence of sentences)
	Basic rules of written composition (eg, punctuation, capitalization)
Grades ≥6	Skills listed for grades 2–5
	Taking notes from lecture
	Paragraph and essay structure
	Different styles and purposes of writing
	Complex grammar structures
	Use of cohesive ties between sentences and paragraphs (eg, pronouns; connector terms such as *however, therefore, in contrast*)
	Editing and proofreading

- Evaluation goals are
  - Rule out other plausible causes.
  - Document specific patterns and severity of learning deficits.
  - Identify significant comorbid conditions.
  - Identify learning strengths.
- Through IDEA, public school systems must provide free evaluations of public and private school students with possible LD.
- Parents can use private resources for evaluations.
  - May provide a more thorough picture of the child's learning profile and more comprehensive treatment planning
  - Can be expensive and typically is not covered by health insurance
  - Often invaluable in elucidating the child's learning problem
- Pediatricians can help by getting to know local psychologists and remedial learning specialists who specialize in LD assessment and treatment.
- Reauthorization of IDEA in 2004 included sections on educational needs of struggling learners, called response to intervention (RTI).
  - RTI is an educational framework with multiple tiers of progressively more intensive instructional support, based on student need, implemented in regular classroom context.
  - Students not making satisfactory progress in a critical learning skill should receive targeted, small group extra instruction with frequent, brief assessment of progress.
  - With adequate progress, targeted instruction ends; with poor progress, more intensive instruction should ensue.
  - Pediatricians should tell parents that by law specified through IDEA
    - RTI cannot be used to delay or deny comprehensive evaluation of a child with a suspected disability.
    - The parent has the right to request evaluation at any time.

LABORATORY FINDINGS

- Laboratory or other medical studies are generally not needed.
- Use as appropriate to rule out underlying medical conditions that may contribute.
- Additional medical studies should be performed only if the child presents with symptoms other than possible LD.
- Genetic studies generally are not necessary.

IMAGING

- Neuroimaging studies generally are not necessary.

DIAGNOSTIC PROCEDURES

- Any child struggling in school must have comprehensive vision and hearing evaluations to rule out sensory impairment.

CLASSIFICATION

- The psychologist who completes the evaluation should provide specific diagnosis and classification.
- Classification can vary by setting.
  - Public school systems use IDEA classifications.
  - Community setting practitioners use *DSM-5* classifications.
- Under IDEA, public schools must determine whether a child meets criteria for specific learning disability compared with other covered conditions (eg, intellectual or sensory impairment).
- Many children have LDs that do not meet the threshold for IDEA classification and associated educational services.
- A challenging aspect of LD identification or diagnosis is discrepancy between aptitude and achievement.
  - Although almost all practitioners agree that LD is characterized by such discrepancies, establishing specific psychometric criteria remains controversial.
  - Individual states differ in how they operationalize IDEA regulations.
  - Having knowledge of available community LD resources, books, and Web sites is a valuable service that pediatricians can provide.

TREATMENT APPROACH

- LD is not a disease and, thus, there generally is no cure.
- LD is a cognitive condition that should be managed proactively to
  - Limit its adverse effects.
  - Maximize the child's opportunities to achieve at the level of his or her potential.
- Keys to successful outcomes include
  - Early identification and appropriate intervention
  - Education of child and parents about LD
  - Classroom accommodations and specialized instruction
  - Avoidance of blame or characterization as lazy
  - Guidance about homework to avoid battles between child and parents
  - Balance of focus learning weaknesses and strengths or interests

- Strong parental advocacy when the child is young
- Self-advocacy as the child becomes older

SPECIFIC TREATMENTS

- Robust scientific evidence now supports interventions for reading disability (dyslexia).
- 5 critical skills support reading proficiency by the end of third grade for all children.
  - Phonemic awareness (ability to identify and work with individual speech sounds that make up words)
    - ≥80% of those with dyslexia have a core deficit in phonemic awareness.
  - Phonics
  - Vocabulary
  - Fluency
  - Comprehension
- Critical instructional features for dyslexia treatment include
  - Reading instruction that is explicit, sequential, systematic, and intensive.
    - Instruction in "cracking the code" to understand how speech sounds map onto written symbols (letters).
    - Phonemic awareness and phonics are the essential starting point.
  - Instruction must focus explicitly on developing automatic word recognition.
    - Many effective research-based remedial reading programs are widely available.
  - Accommodations are important.
    - Technology plays a major role, and new options are rapidly becoming available.
    - Instructional support decisions and accommodations should be based on
      - Effect and severity of LD at a given time in the child's life
      - Rate of progress
      - Child's perspective
    - Older children and adolescents with LD may be uncomfortable with visible supports or modified academic requirements.
    - Less visible accommodations may make the most sense; balance will likely need adjusting during different developmental stages.
  - Efforts to develop persistence and resilience will help children with LD manage challenges, cultivate goals, and support a favorable prognosis.
    - Pediatricians' encouragement and ability to take the longer-term view can be highly encouraging for families.
- Common instructional supports for learning disabilities include
  - Explicit instruction describing the task and method for completing it
  - Explicit explanation and demonstration of appropriate problem-solving strategies
  - Properly sequenced instruction and step size from simpler to more complex tasks or concepts
  - Emphasis on confusing concepts
  - Shortened assignments
  - Task structuring to reduce complexity (eg, spelling test with words that follow only one spelling pattern, such as short a)
  - Multisensory teaching strategies (visual, auditory, tactile, and kinesthetic)
  - Concrete examples of abstract concepts (eg, manipulative materials to represent numeric concepts, such as addition with regrouping)
  - Immediate corrective feedback
  - Frequent repetition and review
  - Multiple-choice rather than recall testing format
  - Cue cards to reduce memory load (eg, alphabet strip on child's desk as child is learning to write letters, index card with steps for subtraction with regrouping)
  - Separation of longer assignments into smaller steps
  - Graphic organizers (eg, tree diagrams to represent hierarchic concepts, visual mnemonic images)
  - Demonstration of problem-solving strategies (eg, identifying known from unknown key issues, developing sequential steps toward a solution)
- Common accommodations for learning disabilities include
  - Extra time to complete assignments and tests
  - Ability to take tests in a quiet, private room
  - Waiver or modification of foreign language requirement
  - Computer or electronic keyboard in lieu of handwritten assignments and tests
  - Calculator
  - Computer technology to listen to scanned reading materials (eg, Kurzweil Education, WYNN Literacy Software Solution)

- Recorded versions of reading assignments (All types of books, including textbooks, are available through Learning Ally.)
- Speech recognition software to convert speech into print (eg, Dragon NaturallySpeaking)
- Preferential seating
- Copies of teacher notes from lectures
- Copies of notes from a good student notetaker
- Ability to mark answers directly on the test rather than on a separate answer form
- A reader for tests
- Option to answer test questions orally rather than in writing
- Tutors
- Study halls
- Learning strategies classes

WHEN TO REFER

- If there are concerns about LD, the child should undergo evaluation through the public school system or be referred to a community psychologist with current LD expertise.
  - Even if the child has had a public school evaluation, a second opinion by another psychologist may be helpful.
  - School-based evaluations often focus on determining whether the child qualifies for services under IDEA, and parents may have questions or concerns that have not been addressed.

FOLLOW-UP

- Follow-up on child's progress is important.
  - With most LDs, an educational program of sufficient intensity should lead to catch-up growth.
  - Holding steady in one's skills is neither sufficient nor justified in most cases.
- Quick, targeted assessment of key skills every few months.
- Periodic comprehensive reevaluation every few years.
  - Assess progress.
  - Adjust treatment plan according to current needs.
  - Ensure maintenance of gains over time.
- When parents have evidence that school is not meeting the child's educational needs, they need to advocate assertively for appropriate changes.
- Caution parents about unproven therapies and provide information about reputable Web sites and book references.

COMPLICATIONS

- Lack of progress or worsening of adverse effects.
  - Further evaluation or reevaluation is often helpful in such cases.
  - Review nature, intensity, and duration of interventions undertaken.
  - Remedial therapy or tutoring may be needed over and above services provided at school.
- Consider undiagnosed comorbid conditions, particularly ADHD.
- Students who chronically struggle and fail academically are at high risk for dropping out of school and for depression and anxiety.
- The longer a child struggles without assistance, the more difficult the academic situation and the greater the emotional toll on the child and family.

PROGNOSIS

- Individuals with LD can achieve at high levels in all types of employment and professions.
- All but the most severely affected should be expected to complete high school and function as independent adults.
- Many participate in postsecondary education programs.
- Individuals may need accommodations throughout the life span.
- To prevent emotion and behavioral difficulties that result from undiagnosed or poorly treated LD
  - Explicitly acknowledge and nurture each child's strengths and interests within school and through nonschool activities.
  - Simultaneously address LD.

PREVENTION

- Keys to minimizing impairment from LD include
  - Early identification, preferably during the preschool years, of children at risk for learning problems
  - Rapid deployment of research-based intervention for children identified as at risk
  - Ongoing progress monitoring and continued intervention
  - Proactive adjustment of supports as the child becomes older
- Pediatricians are ideally suited to lead this effort.
  - Knowledge and surveillance of child development
  - Familiarity with individual patient families
  - Ability to identify science-based treatments
  - Status among parents as a trusted professional

- During the preschool years, guidance on basic child development best practices can help with kindergarten readiness.
  - Caution against too much screen time.
  - Emphasize importance of print materials in the home and reading daily with children.
- Reach Out & Read significantly increases oral language skills in low-income preschoolers and home literacy activities of their parents.
  - Begins at 6 months of age
  - Easy to implement in a pediatric practice
  - Highly cost-effective
- Preschool children can be screened on early literacy skills with Get Ready to Read (GRTR), available online for free in English and Spanish.
  - Research with GRTR shows that intensive early literacy instruction results in significant and sustained early literacy gains.
- Targeted parent intervention shows promise for preventing reading problems.

Limp

DEFINITION

- Abnormal gait pattern
  - Common presenting symptom in pediatric primary care offices and emergency departments

HISTORY

- Careful history is crucial in narrowing the differential diagnosis.
- The physician should first rule out any known trauma.
- Most important to diagnosis
  - Duration
    - Acute onset indicates a mechanical problem, specific hip disorder, or transient infectious process.
    - Limp that lasts for >6 weeks is more consistent with chronic causes, such as juvenile idiopathic arthritis (JIA) or malignancy.
  - Location
    - Ask for a specific location of the pain; child may point with one finger.
    - Consider that some pain in the lower extremity is referred.
    - Hip pathology is generally reported as groin pain but also can be referred to the knee.
    - Pain over the greater trochanter is less likely from pathology of the hip itself and may represent inflammation of the trochanteric bursa (rare in children) or enthesitis.
    - Pain specific to the bone shaft outside the setting of trauma is more concerning for malignancy or focal lesions and less consistent with joint pathology.
  - Timing of symptoms
    - Limp that occurs in the morning and resolves as the day goes on is characteristic of inflammatory joint pain, as seen in arthritis.
    - Pain or limp that worsens with activity is more likely to be from biomechanical factors secondary to trauma or overuse.
    - Unilateral pain that wakes the child at night is worrisome for malignancy or osteoid osteoma.
  - Severity
    - Pain that is severe or limits activity or function is concerning.
  - Systemic symptoms
    - History of fever or weight loss suggests an infectious, oncologic, or inflammatory cause.
    - History of rash may give helpful clues to the diagnosis, eg, systemic JIA, Lyme arthritis, parvo-associated arthritis, or Henoch-Schönlein purpura.

PHYSICAL EXAMINATION

- See Differential Diagnosis section for specific physical examination findings by condition.
- Does the patient appear ill?
  - Ill appearance may be associated with an urgent problem, such as a septic joint or a systemic disease.
  - Any indication of systemic illness warrants a complete examination.
- In the absence of systemic signs, most of the examination can be directed toward the back and lower extremities.
  - Extent and focus of the physical examination should be tailored based on the patient's history.
  - Thorough neurologic assessment should be performed.
    - Include evaluation of muscle strength and function, sensation, and reflexes.
  - Rashes or lesions suggestive of specific disorders should be sought.
  - Complaints of thigh or knee pain may be referred from a hip process and require thorough evaluation of the hip.
- Gait.
  - Distinguishing a limp in a young child can be particularly challenging.
    - Mature gait cycle does not fully develop until >7 years.
    - Much useful information may be gained by opportunistic observation of the child before entering the examination room or when engaged in other activities.
  - Normal, mature, synchronous gait.
    - Stance phase (weight-bearing phase) begins with the heel-strike and plantar-flexion and ends with toe-off.
    - Swing phase starts with toe-off and finishes with heel-strike; requires forward rotation, pelvic tilt, and lumbar spine stability to ensure coordinated gait.
    - Determining the phase of gait affected can help elucidate the cause.
- Joint and musculoskeletal examination.
  - General inspection and palpation of the lower extremities along all surfaces for evidence of skin breakdown, ecchymosis, erythema, or swelling
    - May help localize the problem.
    - Each joint of the lower extremity should be evaluated independently for trauma or inflammation.

- Use the non-affected limb for comparison.
- Range of motion, size, and contour should be symmetric.
- If joint involvement is suspected, joints of the upper extremities and spine should be fully evaluated.

- Leg length.
  - Measure from the anterior superior iliac spine to the distal end of the ipsilateral medial malleolus.
  - Side-to-side disparity in leg length or muscle bulk suggests chronicity.
- Sacroiliac (SI) joint (where the sacrum attaches to the ilium).
  - Joint can be palpated directly under the dimples of Venus.
  - Gaenslen maneuver tests for inflammation of the SI joint.
    - Patient hangs one leg off the table and pulls the opposite knee toward the chest.
    - Test result is considered positive if the patient has pain in the buttock opposite the knee being held.
- Hip joint.
  - Children with hip pathology tend to hold the joint in a flexed, abducted, and externally rotated position, taking pressure off the joint.
  - Isolate the hip joint using the log-roll maneuver.
    - Examiner places a hand on the mid-thigh and mid-shin of the patient and gently rolls the hip internally and externally.
    - Take care not to simultaneously manipulate the knee joint.
- Knee joint.
  - Compare with the contralateral knee to assess for swelling.
    - Often manifests as loss of bony landmarks
  - Assess for warmth and tenderness, pain on motion, or limitation of motion with flexion or extension.
  - Patellofemoral syndrome (formerly known as chondromalacia patella).
    - Patellar inhibition test: Examiner applies pressure to the patellar tendon proximal to the patella while patient tenses the quadriceps muscles; positive result reproduces the patent's pain.
  - Anterior cruciate ligament (ACL) injury.
    - Anterior drawer test: With the patient lying flat and the knee bent at 90°, the examiner pulls the calf forward; if the tibial excursion is greater than normal, the test is considered positive and suggests loss of ACL integrity.
    - Lachman test: Knee is placed at 30° of flexion; while the femur is stabilized with one of the examiner's hands, the tibia is pulled anteriorly with the other hand; if there is no clear end point of anterior movement, or absence of a "clunk," the result is considered positive.
  - Posterior cruciate ligament (PCL) injury.
    - Posterior drawer test: Performed similarly to the anterior drawer test, but the shin is pushed posteriorly; excessive posterior movement suggests PCL injury.
  - Lateral collateral ligament (LCL) and medial collateral ligament (MCL) injuries.
    - Patient lies flat on the back with the knee held at 30° of flexion; shift the shin from side to side to test the integrity of the LCL (varus stress) and MCL (valgus stress).
  - Meniscal injury.
    - Palpate over the joint line for tenderness.
    - McMurray test—medial meniscus: Patient lies in supine position with the knee in full flexion; with one hand, the examiner stabilizes the joint, applying pressure to the lateral aspect of the joint providing valgus stress, while with the opposite hand the examiner holds the heel of the patient and laterally rotates the tibia while extending the knee.
    - McMurray test—lateral meniscus: The medial meniscus is stabilized with one hand while the tibia is rotated medially and the knee is extended by the examiner's other hand.
    - If the patient feels pain or the examiner feels a snap or click, the McMurray test result is positive.
- Ankle.
  - Comprises 2 joints, the tibiotalar joint and the subtalar joint
    - Tibiotalar joint is responsible for dorsiflexion and plantar flexion.
    - Subtalar joint is responsible for inversion and eversion.

DIFFERENTIAL DIAGNOSIS

Trauma

- Most common cause of limp.
- If the mechanism of injury described by the parent or child does not correlate with the physical findings, non-accidental trauma should be considered.

Vascular

- Legg-Calvé-Perthes disease
  - Characterized by avascular necrosis of the femoral head.
  - Patients present with groin or referred knee pain and an antalgic limp, with increased pain on activity.
  - On examination, they generally have pain and limitation on internal hip rotation.
- Osteochondritis dissecans
  - Results from ischemia of the subchondral bone.
  - Can occur in multiple joints, although the knee is the most common.
  - Patients usually present with knee pain, swelling, and sensation of the knee giving way.
  - Pain on motion is characteristic.

Infectious

- Septic arthritis (infection within the joint space)
  - Among the most emergent causes of a limp.
    - Requires rapid identification and treatment to avoid long-term damage and disability
  - Onset of pain is usually rapid.
    - Accompanied by a fever and refusal to bear weight.
    - Joint is generally swollen, warm, tender, and extremely painful with range of motion.
    - With hip infection, swelling and warmth may not be apparent, and pain may be referred toward the knee.
  - Can result from primary infection of contiguous bone (osteomyelitis).
  - In toddlers, the most common organism is *Staphylococcus aureus*.
    - *Haemophilus influenzae,* which in the past accounted for ~70% of cases, has been virtually eliminated by universal immunization.
    - *Kingella kingae* is being identified more frequently than in the past as a cause of septic arthritis and osteomyelitis in young children.
  - In infants <2 months, group B streptococcus is the most common organism.
  - In adolescents, *S aureus* remains the most common organism, but with sexual activity, gonococcal arthritis becomes a consideration.
- Osteomyelitis
  - Most commonly results from hematogenous seeding.
  - May follow penetrating trauma or deep contiguous infection, as may occur with decubitus ulcers.
  - Involvement of long bones is most common (femur or tibia).
  - Patients often present with fever and pain in the affected extremity and limp and may report preceding trauma.
  - Physical examination findings depend on the location of the infection.
    - Point tenderness over the bony metaphysis is highly suggestive of osteomyelitis.
  - Usually caused by the same organisms as septic arthritis.
    - *Pseudomonas aeruginosa* is a notable pathogen following nail puncture wounds of the foot, particularly through the soles of sneakers.
    - Children with sickle cell disease are at particular risk for osteomyelitis, most often from *Salmonella.*
- Diskitis
  - Patients limp or refuse to walk, sit, or perform any motion that requires range of motion of the affected region of the spine.
  - Physical examination reveals pain over the involved disc space and decreased range of motion of the spine.
  - The child generally does not seem ill or febrile.
  - *S aureus* is the most common pathogen.
- Intra-abdominal infection
  - Appendicitis and psoas abscess can manifest with limp.

Malignancy or Tumor

- Leukemia
  - Presents with musculoskeletal pain in 15%–30% of cases.
  - Limp is usually accompanied by systemic symptoms, including fever, pallor, and fatigue.
  - Pain may awaken the patient from sleep and is generally out of proportion to findings on clinical examination.
  - Physical examination may reveal frank arthritis, bone tenderness, or bone pain.

- Thrombocytopenia and night waking help differentiate malignancy from systemic JIA, which can also manifest as joint pain with systemic symptoms.

- Osteosarcoma—malignant tumor
  - Patients often report night waking with pain and tenderness at the affected site.
- Osteoid osteoma—benign tumor
  - Patients typically have localized pain that is worse in the evenings and responds dramatically to nonsteroidal anti-inflammatory drugs (NSAIDs).
  - If left untreated, the tumor can cause asymmetric limb growth.

Skeletal Anomaly

- Congenital hip dysplasia
  - Most commonly diagnosed in infancy but can manifest as a delay in walking or as an abnormal gait in the toddler
  - Typically decreased abduction and extension of the affected hip
  - One-sided toe walking to compensate for an apparent leg-length discrepancy
- Discoid meniscus
  - Lateral meniscus is discoid rather than crescent shaped.
  - Patients often report pain with activity.
  - On physical examination, swelling of the knee or inability to fully extend the knee.
  - Tenderness along the lateral joint line.
- Tarsal coalition
  - Abnormal ossification between the talus or navicular and the calcaneus.
  - Often associated with foot pain.
  - Physical examination reveals a stiff, flat foot in eversion with contracture of the peroneal muscles.
- Slipped capital femoral epiphysis (SCFE)
  - Femoral epiphysis slides posteriorly, resulting in limited internal rotation of the hip.
  - Symptom onset can be acute or insidious with weeks to months of intermittent vague symptoms.
  - Associated conditions include
    - Hypothyroidism
    - Low growth hormone level
    - Pituitary tumors
    - Craniopharyngioma
    - Down syndrome
    - Renal osteodystrophy
    - Adiposogenital syndrome

Inflammatory Disease

- JIA
  - General term used to describe arthritis lasting >6 weeks in a child or teen ≤16 years with no known cause.
    - Specific subtype is determined by the number of and specific joints involved, associated systemic symptoms, and HLA-B27 positivity.
    - Age of onset varies by subtype.
  - Symptoms at onset include joint pain and swelling, limp, morning preponderance of pain, and morning stiffness.
    - Systemic JIA may include fever and rash.
  - One or more joints is affected, most commonly the knee.
    - Pain over the Achilles tendon or at the sites of attachment of the plantar fascia in the setting of chronic pain may be associated with enthesitis related to JIA.
    - SI joint is often involved in one of the subtypes of JIA: enthesitis-related JIA.
  - If present, leg-length discrepancy and muscle atrophy of the affected extremity suggest a chronic process.
- Systemic lupus erythematosus (SLE)
  - Chronic autoimmune disease affecting multiple organs, associated with antinuclear antibodies (ANAs).
  - Symptoms include a nonerosive arthritis, which can present with a limp.
- Transient synovitis
  - Most often presents as hip arthritis; pain on motion of the hip with mild limitation.
    - Patient is not otherwise ill appearing.
  - May be preceded by viral infection.
    - Generally less symptomatic than septic arthritis, without associated fever
  - Lasts for 7–10 days, generally resolving spontaneously.
- Juvenile dermatomyositis (JDM)
  - Chronic autoimmune inflammatory myopathy and vasculopathy.
  - Patients typically present with a heliotrope rash, Gottron papules (violet-colored inflammatory lesions over the knuckles), and proximal muscle weakness.
  - Arthritis can also occur.

Neuromuscular Disorder

- Cerebral palsy (CP)
  - Nonprogressive motor disorder.
  - Highly variable.
  - Physical examination may reveal spasticity of the knee or ankle joint with hyperreflexia and clonus.
- Muscular dystrophy
  - Often first manifests as delayed walking.
  - The patient may demonstrate toe walking and a positive Gower sign (inability to rise from the floor without leaning on his legs with his hands), as well as proximal muscle weakness.

LABORATORY EVALUATION

Laboratory Tests by Presumed Diagnosis

- Trauma
  - Blood testing is not usually necessary in the setting of known trauma.
- Inflammation or infection
  - Complete blood cell count (CBC) and acute phase reactants (erythrocyte sedimentation rate [ESR], C-reactive protein [CRP]).
  - ANA testing in the absence of objective evidence of arthritis is not necessary without additional clinical findings suggestive of autoimmune disease (vasculitic/malar rash, palatal ulcers, hair loss, serositis, renal or central nervous system disease).
    - In chronic arthritis, ANA is useful but not diagnostic in determining risk of developing uveitis.
    - ~20% of healthy children have a positive ANA without any underlying disease.
  - If arthritis is seen on physical examination and history is suggestive, the following titers and cultures may be warranted:
    - Lyme
    - Gonococci
    - Parvovirus immunoglobulin G (IgG) and IgM
    - Anti-deoxyribonuclease B
    - Anti-streptolysin O
- Septic arthritis and osteomyelitis
  - CBC
  - ESR, CRP
    - ESR <20 mm/h or normal CRP lowers the likelihood of serous infection but does not exclude skeletal infection.
  - Blood cultures prior to initiation of antibiotics
  - Synovial fluid evaluation (with Gram stain, culture, and cell count)
    - Etiologic agents are isolated in blood or synovial fluid in 34%–82% of cases.
    - Synovial fluid generally reveals elevated white blood cell (WBC) count with increased segmented neutrophils.
- Diskitis
  - ESR and CRP are typically elevated.
- Leukemia
  - Abnormally high or low WBC count with anemia and thrombocytopenia
- JIA
  - Laboratory evaluation excludes other causes of arthritis and assesses inflammatory markers.
  - CBC.
  - ESR.
  - CRP.
  - Lyme serology (only in those from or who visited endemic areas).
  - Arteriosclerosis obliterans.
  - Parvovirus.
  - Once the diagnosis of JIA is made, additional laboratory tests can help clarify subtype.
    - Rheumatoid factor
    - Anti-cyclic citrullinated peptide antibody
    - ANA
    - HLA-B27 typing
- SLE
  - If other symptoms of lupus are present and the index of suspicion is high
    - ANA
    - CBC
    - Urinalysis
  - Workup as previously described to rule out infectious causes of arthritis.
- Transient synovitis
  - Inflammatory markers may be normal or only mildly elevated.
- JDM
  - Muscle enzymes are elevated.
- Muscular dystrophy
  - Serum creatine phosphokinase is elevated.

IMAGING

- Imaging should be guided by the history and physical examination.
  - Magnetic resonance imaging (MRI) is the imaging modality of choice for clarifying difficult diagnoses.

- Radiography (plain film).
  - Useful to diagnose
    - Fractures
    - Hip disease
    - Spinal abnormalities
    - Foot disease (eg, tarsal coalition)
  - ≥2 views of affected area are essential.
  - Suspected hip disease.
    - Anteroposterior and frog-leg lateral (Lauenstein) views of the pelvis
  - Legg-Calvé-Perthes disease.
    - Early in the course, radiography may be normal or may show increased density of the femoral head on the affected side.
    - Later radiographs will show subchondral lucency, and, ultimately, collapse and destruction of the femoral epiphysis.
  - Osteochondritis dissecans.
    - Plain radiographs reveal a radiolucent zone separating the osteochondral fragment from the rest of the bone.
  - Septic arthritis.
    - Radiographs may reveal a joint effusion.
  - Osteomyelitis.
    - Radiographs are often negative on presentation but generally show abnormalities 10–21 days after onset.
  - Leukemia.
    - Radiographs may reveal leukemic lines, which appear as metaphyseal sclerotic bands, and osteopenia.
  - Osteosarcoma.
    - Radiographs generally show abnormality in the bone, most often in the metaphyses of long bones.
  - Osteoid osteoma.
    - Radiographs typically reveal cortical thickening and sclerosis with <1 cm radiolucent nidus.
    - The nidus is not visible in 15% of cases.
    - If index of suspicion is high, computed tomography (CT), MRI, or bone scan should be pursued to establish the diagnosis.
  - Congenital hip dysplasia.
    - Beyond infancy, the anomaly is visible on standing radiographs.
  - SCFE.
    - Radiographs in the frog-leg position are generally diagnostic.
  - Tarsal coalition.
    - Can often be diagnosed on oblique radiographs of the ankle joint
- Ultrasonography.
  - Used to assess musculoskeletal pathology.
  - Joint effusions, synovial thickening, and increased blood flow seen by power Doppler suggest underlying inflammation.
    - Cause of inflammation cannot be determined by this method, although it may be a useful adjuvant to history and physical examination.
  - Congenital hip dysplasia.
    - Generally diagnostic in the newborn period
- Bone scintigraphy.
  - Measures the uptake of technetium 99m, which is increased at sites of high bone turnover.
    - Most useful in diagnosis of osteomyelitis, diskitis, stress fractures, osteoid osteomas, Legg-Calvé-Perthes disease, and neoplasm, especially if pathology is difficult to locate.
  - MRI is often preferred to spare children radiation exposure and to provide more specific information.
- CT.
  - Most useful for evaluating bony pathology, including tarsal coalition, spondylolisthesis, spondylolysis, or osteoid osteoma.
  - Drawbacks include exposure to a high dose of radiation.
    - CT should be limited to situations where other imaging modalities are inadequate or unavailable.
  - Tarsal coalition.
    - If the plain radiograph result is negative but there is a high index of suspicion, CT may be diagnostic.
- MRI.
  - Offers information about bone formation and inflammation as well as soft tissues without exposure to radiation
    - In arthritis, osteomyelitis, diskitis, stress fractures, osteoid osteomas, Legg-Calvé-Perthes disease, and neoplasm, MRI is often crucial to diagnosis.
  - Osteomyelitis
    - MRI may be diagnostic and should be used to guide surgical drainage if subperiosteal abscess is suspected.
  - Discoid meniscus
    - MRI is required for diagnosis.
    - Noncontrast fat-suppressed MRI shows proximal muscle edema.

DIAGNOSTIC PROCEDURES

- Joint aspiration should be performed promptly by an orthopedist if septic arthritis is suspected.

TREATMENT APPROACH

- Unless evaluation suggests fracture or ligament damage, infection, malignancy, skeletal anomaly, inflammatory disease, or neuromuscular disorder, treat with
  - Rest
  - Ice (in initial 48–72 hours after trauma)
  - Compression
  - Elevation
  - Analgesics
- Septic arthritis necessitates emergent orthopedic involvement for diagnosis and therapeutic aspiration.

SPECIFIC TREATMENT

- Trauma
  - Rest, ice, compression, elevation, and analgesics are the mainstays of therapy.
- Infection
  - Septic arthritis
    - Joint aspiration and drainage should be promptly performed in patients with hip or shoulder infection.
    - Gram stain and culture, when positive, guide antibiotic management.
  - Osteomyelitis
    - Involvement of an orthopedist and infectious diseases specialist to obtain culture material and tailor therapy
  - Diskitis
    - Antibiotics and rest
- Skeletal anomaly
  - Congenital hip dysplasia
    - Treatment after the newborn period generally requires surgical intervention.
  - Tarsal coalition
    - Management initially involves rest but may involve surgery in severe cases.
- Inflammatory disease
  - Rheumatologic diseases (JIA, SLE, JDM) should be treated by a specialist.
  - Transient synovitis
    - Rest and NSAIDs

WHEN TO REFER

- Suspicion of any of the following causes warrants referral to pediatric orthopedics:
  - Septic joint
    - Emergent joint aspiration and drainage
  - Fracture, ligament damage, or tendon damage
  - Legg-Calvé-Perthes disease
  - Osteomyelitis
    - An infectious diseases specialist also can be helpful in the choice of antibiotic treatment.
  - Congenital hip dysplasia
  - SCFE
- Refer to a pediatric rheumatologist for suspected
  - JIA
  - SLE
  - JDM
- Refer to a pediatric oncologist immediately for suspected
  - Malignancy, ie, osteosarcoma
- Refer to a pediatric neurologist for suspected
  - CP
    - Also refer to a pediatric physiatrist.
  - Muscular dystrophy
- Refer to a pediatric surgeon for suspected appendicitis or psoas abscess.

WHEN TO ADMIT

- Admission is warranted for
  - Serious bacterial infection (eg, septic arthritis, osteomyelitis, diskitis)
  - Malignancy
  - Orthopedic surgical intervention (eg, SCFE, fractures needing fixation, congenital hip dysplasia)
  - Intra-abdominal infections (appendicitis, psoas abscess)

FOLLOW-UP

- Once emergent causes of limp have been excluded, if the workup is negative, observation for 1–2 weeks may be appropriate.
  - After the observation period, if the diagnosis is still unclear, referral may be necessary.

DEFINITION

- Loss of appetite (anorexia) is a common symptom in children.
- A transient loss of appetite is often associated with acute illness.
- Prolonged loss of appetite, when associated with poor weight gain or weight loss, may signify a serious or chronic illness.
- In infants, it is difficult to differentiate between loss of appetite and poor feeding.
- This is distinct from, but closely related to, failure to thrive.

HISTORY

- Review diet of the child and family, what they consume and how much.
- Adequate evaluation of nutritional intake requires assessment of calories consumed.
- Assess parental expectations.
- Take a careful birth, family, medical, and medication history.
- For infants
  - Ask about sick contacts and exposure to illness.
  - Discuss gastrointestinal (GI) symptoms, such as emesis, constipation, diarrhea, and amount, frequency, and character of stools.
  - Ask about other signs and symptoms indicative of feeding intolerance, including rashes.
  - Compare caloric intake with estimated caloric needs.
  - Assess feeding effort and coordination.
  - If formula feeding
    - Determine how the formula is prepared, the exact proportions of water to powder or concentrate.
    - Calculate total caloric intake: volume of formula × caloric density of formula (standard is 20 kcal/oz).
  - If breastfeeding, assess
    - Perceived adequacy of maternal milk production
    - Ability of infant to breastfeed
- For children and adolescents
  - Assess intake and output.
  - Discuss whether eating leads to symptoms such as pain, emesis, diarrhea, and fatigue.
  - Discuss quantity and type of stools.
  - Assess body image, social context, and stressors.
  - Consider substance abuse.
  - Consider HEADSSS assessment (**h**ome, **e**ducation, **a**ctivities, **d**rugs, **s**exuality, **s**uicide/depression, **s**afety).

PHYSICAL EXAMINATION

- Vital signs
  - Measure temperature, heart and respiratory rates, and blood pressure.
  - Examine for orthostatic changes.
  - Weigh the patient and plot on a growth chart.
    - Consider serial weights for computation of growth velocities.
  - With breastfed infants, consider weighing infant before and after feedings.
  - In children ≥2 years, compute body mass index (BMI), BMI percentile, and weight for length/height.
- Physical examination
  - Assess mental status.
  - Assess volume status and for anemia (eg, pale conjunctiva).
  - Examine oral mucosa for thrush and ulcerations.
  - Examine nose and palate.
  - Assess cardiorespiratory status.
  - Assess the abdomen for organomegaly.
  - Look for signs of malnutrition or vitamin deficiencies (eg, lanugo).
  - Look for clinical findings related to genetic disorders (eg, Down syndrome, Turner syndrome).
  - Oral aphthous ulcers may be related to Crohn disease.
  - Discoloration of teeth may be related to purging behaviors.
  - Assess for toxidromes in adolescents.

DIFFERENTIAL DIAGNOSIS

Newborn Period/Infancy

- Poor oral intake by an infant developmentally capable of feeding has a broad differential diagnosis that includes
  - Infection
    - Sepsis
    - Meningitis
    - Urinary tract infection
    - Congenital viral infection
    - Oral thrush, herpangina
  - Central nervous system disorder
  - Cardiac disease (eg, congestive heart failure, cyanotic heart disease)
  - Structural or functional craniofacial or GI abnormality (eg, choanal atresia, cleft palate, velopharyngeal insufficiency)
  - Renal failure
  - Metabolic or genetic issues (eg, inborn error of metabolism, Down syndrome, Prader-Willi syndrome)

- Endocrine disorders (eg, congenital hypothyroidism)
- Drug intoxication (including maternal substance abuse and perinatal administration of opioids or magnesium)

Childhood and Adolescence

- Infections, acute or chronic
- Neurologic causes
  - Cerebral palsy
  - Congenital degenerative disease (eg, neurodegenerative disorders, spinomuscular atrophy, muscular dystrophy)
  - Hypothalamic lesion
  - Increased intracranial pressure, including brain tumor
  - Static encephalopathy
- Cardiac causes
  - Congestive heart failure
  - Cyanotic heart disease
- GI causes
  - Significant GI disease commonly leads to poor appetite.
    - However, anorexia may result from disease that is distant from the bowel.
  - Oral or esophageal lesions (eg, thrush, herpes simplex, dental caries, ankyloglossia).
  - Gastroesophageal reflux.
  - Eosinophilic esophagitis.
  - Dietary protein intolerance.
  - Bowel obstruction, especially with gastric or intestinal distention.
  - Short bowel syndrome.
  - Inflammatory bowel disease.
  - Celiac disease.
  - Cystic fibrosis.
  - Constipation.
  - Esophageal motility disorder (eg, cricopharyngeal dysfunction, achalasia, connective tissue disorder).
- Metabolic causes
  - Renal failure, renal tubular acidosis, or both
  - Liver failure
  - Inborn errors of metabolism
  - Lead poisoning
- Endocrine causes
  - Hypothyroidism
  - Adrenal insufficiency
  - Hyperparathyroidism
- Nutritional causes
  - Marasmus
  - Iron deficiency
  - Zinc deficiency
- Drugs
  - Morphine
  - Digitalis
  - Antimetabolites
  - Methylphenidate
  - Amphetamines
  - Topiramate
- Prolonged restriction of oral feedings, beginning in the neonatal period
  - The neonate may not be interested when feedings are introduced by mouth.
  - Mother and baby may require training.
    - Typically provided by occupational therapist, physical therapist, or speech pathologist.
    - The neonate may require gradual advancement of the oral diet.
- Tumor
- Chronic febrile conditions (eg, rheumatoid arthritis, rheumatic fever)

Psychological Factors

- Emotional deprivation.
  - Common cause of failure to thrive.
  - Thorough social history is essential to the evaluation.
  - Early observation of parent-neonate interaction in the hospital, including feeding techniques, may be helpful.
- Anxiety, fear, depression, or mania (limbic influence on the hypothalamus) may affect feeding.
- If meals produce discomfort (eg, abdominal pain, nausea, diarrhea, bloating, urgency, dumping syndrome), poor feeding may be a result of avoidance.
- Anorexia nervosa.
- Excessive weight loss and food aversion in athletes, simulating anorexia nervosa.

LABORATORY EVALUATION

- Evaluation is guided by clinical suspicion.
- In infants, ensure that newborn screening has been performed.
- Because the differential diagnosis is broad, the workup is nonspecific.
- Studies may include
  - Blood chemistries
  - Complete blood cell count
  - Blood, cerebrospinal fluid, and urine for
    - Viral studies
    - Bacterial studies
  - Stool studies for
    - Reducing substances
    - Collections for fat quantification
    - Guaiac

- Serum studies
  - Ammonia
  - Liver function tests (including albumin)
  - Vitamin and mineral levels
  - Celiac panel
- Serum and urine amino/organic acid testing
- Therapeutic drug monitoring
- Toxin screens
- Chromosome count
- Specific genetic testing

IMAGING

- Imaging is guided by clinical suspicion.

DIAGNOSTIC PROCEDURES

- Diagnostic procedures may be performed as guided by clinical suspicion.
  - Upper endoscopy with biopsy
  - Colonoscopy
  - Sweat chloride testing
  - Esophageal motility testing
  - pH probes

TREATMENT APPROACH

- Serial evaluations of weight and intake are the cornerstones of assessing appetite.
- Assess parental expectations to ensure that they are realistic, especially in the setting of a normal growth pattern.
- If growth is poor, a systematic evaluation in the case of failure to thrive can be extensive.
- Includes
  - Assessment of bone age (imaging or teeth)
  - Parental growth patterns
  - Mid-parental height
  - Nutrition
  - Environmental influences

SPECIFIC TREATMENT

- Treatment that improves symptoms may result in rapid improvement in oral intake.
- In infants, lactation consultation as indicated and available.
- Enlist the help of a nutritionist to plan diets and supplementation.
  - Foods more acceptable to the child
  - High-calorie milkshakes or snacks
  - Commercial high-calorie supplements
- Medications can be used to stimulate appetite.
- Occasionally, children will require feeding supplementation.
  - Consider placement of nasogastric, gastric, and jejunal feeding tubes.

Appetite Stimulants

- Cyproheptadine.
  - Does not seem to affect appetite in all children treated.
  - When successful, response is dramatic.
- Megestrol acetate.
  - Progesterone derivative.
  - Has been administered for cancer-related anorexia, primarily in adults.
  - Potential side effects include adrenal insufficiency.
  - Weight gained may be largely from increased fat mass.
- Eicosapentaenoic acid, an omega-3 fatty acid, has been evaluated in treatment of cancer-associated anorexia with equivocal results.

Feeding Supplementation

- Initial nasogastric or nasoduodenal nutrient infusion.
  - May be necessary to promote growth in some disorders (ie, congenital heart disease).
  - Place gastrostomy tube if prolonged supplementation is required.
- Parenteral nutrition.
  - May be indicated in specific situations.
  - Expertise with this modality and close supervision are required.
  - Caregivers need special training if parenteral nutrition is to be provided at home.
- Refeeding after severe malnutrition requires careful consideration of potential cardiac and metabolic complications and may require inpatient monitoring.

WHEN TO REFER

- Loss of appetite without an obvious explanation, especially in association with weight loss or failure to thrive
- Anorexia nervosa

WHEN TO ADMIT

- Weight loss or lack of weight gain unresponsive to outpatient management
- To initiate enteral or parenteral feeding because of inadequate oral intake
- Significant metabolic derangements caused by prolonged malnutrition

FOLLOW-UP

- Patients with failure to thrive need close monitoring of their caloric intake and weight gain.

Lyme Disease

DEFINITION

- Lyme disease is a tick-borne infectious disease.

SIGNS AND SYMPTOMS

- The clinical manifestations of Lyme disease vary with the time that elapses after inoculation by the tick.
- The infection has thus been divided into
  - Early localized phase
  - Early disseminated phase
  - Late-stage disease

Early Localized Phase

- Erythema migrans (EM) is the most common manifestation of early Lyme disease.
- EM typically appears within 7–14 days (range, 3–30 days) of the tick bite and, if untreated, resolves within 3–4 weeks.
- ~70%–80% of patients exhibit or have a history of a skin lesion at the site of the tick bite.
- Macule gradually expands over several days to a large erythematous lesion that may increase in size to ≥30 cm, sometimes with central clearing.
- Early lesions may not have central clearing or the characteristic target-like appearance.
- A small bump or redness at the site of a tick bite that occurs immediately is common and usually goes away in 1–2 days; this is not a sign of Lyme disease.
- Rash may be warm but is not usually painful or itchy.
- Influenza-like symptoms may accompany the skin lesion, including
  - Malaise
  - Fatigue
  - Headache
  - Arthralgia
  - Myalgia
  - Fever
  - Regional lymphadenopathy
- Cough, rhinorrhea, vomiting, or diarrhea is not typical.

Early Disseminated Phase

- In the absence of antimicrobial therapy, hematogenous spread of the spirochete *may* occur, producing the disseminated phase of early Lyme disease.
- Within days or weeks, in an untreated person, early disseminated disease may produce
  - Multiple secondary EM lesions
  - Bell palsy
  - Lymphocytic meningitis
  - Conjunctivitis
- Common systemic symptoms include
  - Arthralgia
  - Myalgia
  - Headache
  - Fatigue
- ~60% of untreated patients will develop monoarticular or oligoarticular migratory arthritis, which generally involves the knees.
- ~5%–10% of untreated patients will develop neurologic manifestations.
  - Nervous system involvement may include
    - Cranial neuropathy (especially unilateral or bilateral facial palsy)
    - Radiculopathy
  - Central nervous system (CNS) involvement may include lymphocytic meningitis.
  - Encephalopathy associated with late-stage Lyme disease consisting of mild abnormalities of memory and cognitive function is poorly understood and is a rare occurrence.
- <5% of untreated patients will develop cardiac disease.
  - Cardiac involvement is characterized most commonly by varying degrees of atrioventricular block but may include myopericarditis.
  - Hospitalization is appropriate for patients with syncope, dyspnea, or chest pain.
  - Complete heart block is usually brief, and only temporary cardiac pacing is needed.
- In untreated persons, symptoms involving the joints, CNS, or heart, reflecting spread of the spirochete to other parts of the body, may occur months after the tick bite.
- Other symptoms may include
  - Intermittent pain in tendons and muscles
  - Conjunctivitis, keratitis, uveitis
  - Mild hepatitis
  - Splenomegaly

Late-Stage Disease

- Late-stage disease most commonly produces recurrent oligoarticular arthritis that involves the knees.
- Peripheral or CNS involvement is rare.
- Late-stage disease is uncommon in children who receive antimicrobial therapy early in the disease.

DIFFERENTIAL DIAGNOSIS

- The same tick that transmits *Borrelia burgdorferi* also can transmit *Anaplasma phagocytophilum* (the agent of ehrlichiosis) and *Babesia microti* (the agent of babesiosis), either as a mixed infection or as a single infection.
  - Ehrlichiosis or anaplasmosis should be suspected in the appropriate epidemiologic setting in a patient with
    - Fever
    - Chills
    - Headache
    - Thrombocytopenia
    - Leukopenia
    - Increased liver enzyme levels
  - Babesiosis in symptomatic patients may produce
    - Fever
    - Malaise
    - Chills
    - Sweating episodes
- The lone star tick bite can cause a similar EM rash along with flu-like symptoms.
  - Etiology unknown.
  - Unknown if treatment with antibiotics makes a difference.
  - Tick can be found from Texas to Oklahoma eastward to the Atlantic coast and as far north as Maine.
- Additional differential diagnoses include
  - Oligoarticular juvenile arthritis
  - Septic arthritis
  - Acute rheumatic fever
  - Fibromyalgia syndrome
- Other considerations include
  - Aseptic meningitis caused by enterovirus infection
  - Bell palsy caused by herpes simplex
  - Varicella-zoster virus
  - Epstein Barr virus or mycoplasma
  - A peripheral neuropathy not caused by *B burgdorferi*
  - Multiple sclerosis

Post-Lyme Syndromes

- Considerable confusion surrounds this topic in part because of the lack of a widely accepted definition.
- A recent report from the Infectious Diseases Society of America confirmed the following conclusions:
  - There is no convincing biologic evidence for the existence of symptomatic chronic *B burgdorferi* infection among patients after receipt of a recommended treatment regimen.
  - Antibiotic therapy has not proven to be useful and is not recommended for patients with chronic (>6 months) or subjective symptoms after a recommended treatment regimen for Lyme disease.

DIAGNOSTIC APPROACH

- Some patients with Lyme disease may offer no history of a tick bite or EM.
- During spring and summer months in an endemic area, Lyme disease should be considered in a patient who has lymphocytic meningitis or arthritis involving the knee.
- EM can be diagnosed in a person who lives in or has traveled to an endemic area and is a sufficient basis for a clinical diagnosis without laboratory confirmation, as blood value is usually negative at time of rash.

LABORATORY FINDINGS

- Serum antibody to *B burgdorferi* is usually not present during the early stage, requiring 3–4 weeks to appear.
  - As many as 60% of cases will have a false-negative test result.
- The spirochete is cultured from the skin more easily during early infection than at any other time in the illness.
  - However, culture media are not widely available and sensitivity is low.
- Serologic testing may be useful in the few patients in whom a diagnosis is uncertain, particularly when symptoms have been present for more than several weeks.
- A 2-tier approach to serologic testing for Lyme disease should be used with acute- and convalescent-phase serum specimens.
  - Initial testing is conducted using an enzyme immunoassay (EIA).
    - This step should not be skipped, as it leads to increased frequency of false-positive results on Western blot.
    - The second test is necessary, as EIAs have low specificity/high sensitivity and may yield false-positive results.
      - They may cross-react with antibodies to commensal or pathogenic spirochetes (particularly anaplasmosis, previously known as ehrlichiosis), some viral infections (eg, varicella, Epstein-Barr virus), or certain autoimmune diseases (eg, lupus erythematosus).

- If positive or equivocal results are obtained on EIA, a standardized Western immunoblot for Lyme-specific immunoglobulins should be performed, using the same serum specimen for tier 1 and tier 2 testing.
  - If the patient has been symptomatic for <30 days, immunoglobulin M (IgM) and IgG should be tested.
  - If the patient has been symptomatic for >30 days, only the IgG should be done, as IgM testing leads to more false-positive results at this stage.
  - An IgM immunoblot is considered positive if 2 of 3 bands are present.
  - An IgG immunoblot is defined as positive if 5 of 10 bands are detected.
  - Less than this number of bands is not a "mild" or "somewhat positive" case but considered negative for the disease.

- Laboratory testing should *not* be performed for people who do not have symptoms consistent with Lyme disease.
- Laboratory testing should *not* be done to assure cure, as Lyme-specific immunoglobulins are long lasting in duration and do not correlate with current disease state after treatment.
- Testing of individual ticks is not useful for deciding whether antibiotic therapy (treatment or prophylaxis) should be initiated after a tick bite.
- Other laboratory tests that should *not* be used include
  - Urine antigen assays
  - Immunofluorescence staining for cell wall–deficient forms of *B burgdorferi*
  - Lymphocyte transformation assays
  - Quantitative CD57 lymphocyte assays
  - "Reverse Western blots"

IMAGING

- Imaging is not recommended with the diagnosis of Lyme disease.
- For a swollen joint, consider radiograph to rule out other causes on differential diagnosis.

DIAGNOSTIC PROCEDURES

- Consider joint aspiration for other causes on differential diagnosis.

CLASSIFICATION

- The infection can be classified as
  - Early localized phase
  - Early disseminated phase
  - Late-stage disease

TREATMENT APPROACH

- Early use of appropriate antibiotics usually results in resolution of symptoms.

SPECIFIC TREATMENTS

Pharmacotherapy

- Patients ≥8 years with early localized or early disseminated disease who do not have neurologic or cardiac involvement should be treated for 14–21 days with doxycycline.
  - Pregnant or lactating women should not be treated with doxycycline.
  - An advantage of doxycycline is efficacy against anaplasmosis, which may be a coinfecting microbe.
- Amoxicillin should be used for children <8 years and in pregnant women.
- Cefuroxime axetil is a third drug of choice for patients not able to take preferred agents.
- Clinical trials of patients with EM show resolution of symptoms in >90% of patients treated with doxycycline, amoxicillin, or cefuroxime axetil.
- Macrolide antibiotics are less effective than other antimicrobial agents and should be reserved for patients who cannot take preferred agents.
- Intravenous versus oral.
  - Ceftriaxone is *not* superior to oral agents, *except* in patients with neurologic or cardiac involvement.
  - Oral antimicrobial agents are effective for treating multiple EM and uncomplicated Lyme arthritis.
  - Oral agents can be used to treat most people with facial nerve palsy.
  - CNS involvement, such as meningitis, should be treated with parenteral antibiotic therapy.
  - Although first-degree atrioventricular block usually responds to oral therapy, higher-grade blocks are usually treated with parenteral ceftriaxone or penicillin.
  - Persistent or recurrent arthritis should be treated with parenteral ceftriaxone or penicillin.
- Specific dosages and durations are given in **Table 1.**

Prophylaxis After a Tick Bite

- Clinical practice guidelines for prevention of Lyme disease after a tick bite suggest that the following conditions be satisfied:
  - The biting tick is identified as *Ixodes scapularis,* with an estimated attachment time >36 hours based on the size of the engorged tick.

Table 1. Treatment Regimens for Lyme Disease

Disease Category	Drugs(s) and Dose[a]
Early Localized Disease[a]	
≥8 y	Doxycycline, 4 mg/kg/d, orally, divided into 2 doses (maximum 200 mg/d) for 14 days[b]
<8 years or unable to tolerate doxycycline[b]	Amoxicillin, 50 mg/kg/d, orally, divided into 3 doses (maximum 1.5 g/d) for 14 days **OR** Cefuroxime, 30 mg/kg/d in 2 divided doses (maximum 1,000 mg/d or 1 g/d) for 14 days
Early Disseminated and Late Disease	
Multiple erythema migrans	Same oral regimen as for early localized disease, for 14 days
Isolated facial palsy	Same oral regimen as for early localized disease, for 14 days (range 14–21 days)[c,d]
Arthritis	Same oral regimen as for early localized disease, for 28 days
Recurrent arthritis	Same oral regimen as for first-episode arthritis, for 28 days **OR** Preferred parenteral regimen: ceftriaxone sodium, 50–75 mg/kg, IV, once a day (maximum 2 g/d) for 14 days (range 14–28 days) Alternative parenteral regimen: penicillin, 200,000–400,000 U/kg/d, IV, given in divided doses every 4 h (maximum 18–24 million U/d) for 14 days (range 14–28 days) **OR** Cefotaxime 150–200 mg/kg/d, IV, divided into 3 or 4 doses (maximum 6 g/d) for 14 days (range 14–28 days)
Antibiotic-refractory/ persistent arthritis[e]	Symptomatic therapy
Atrioventricular heart block or carditis	Oral regimen as for early disease if asymptomatic[f] or not hospitalized, for 14 days (range 14–21 days) **OR** Parenteral regimen initially for hospitalized patients, dosing as for recurrent arthritis, for 14 days (range 14–21 days); oral therapy can be substituted to complete the 14–21 day course.
Meningitis	Ceftriaxone[g] or alternatives of cefotaxime or penicillin[g]: dosing as for recurrent arthritis, for 14 days (range 10–21 days) **OR** Doxycycline, 4–8 mg/kg/d, orally, divided into 2 doses (maximum 100–200 mg) for 14 days (range 14–21 days)[b]

Table 1 (*continued*)

Disease Category	Drugs(s) and Dose[a]
Encephalitis or other late neurologic disease[h]	Ceftriaxone[g] or alternatives of cefotaxime or penicillin[g]: dosing as for recurrent arthritis, for 14 days (range 14–28 days)

Abbreviation: IV, intravenously.

[a] For patients who are allergic to penicillin, alternatives are cefuroxime, azithromycin, and erythromycin.
[b] Tetracycline-based antimicrobial agents, including doxycycline, may cause permanent tooth discoloration for children <8 years if used for repeated treatment courses. However, doxycycline binds less readily to calcium compared with older tetracyclines and, in some studies, doxycycline was not associated with visible teeth staining in younger children.
[c] Corticosteroids should not be given.
[d] Treatment has no effect on the resolution of facial nerve palsy; its purpose is to prevent late disease.
[e] Arthritis is not considered persistent unless objective evidence of synovitis exists at least 2 months after completion of a course of parenteral therapy or of two 28-day courses of oral therapy. Some experts administer a second course of an oral agent before using an IV-administered antimicrobial agent.
[f] Symptoms for heart block or carditis include syncope, dyspnea, or chest pain.
[g] For treatment of meningitis or encephalitis with ceftriaxone, cefotaxime, or penicillin, drug should be administered IV.
[h] Other late neurologic manifestations include peripheral neuropathy or encephalopathy.

From American Academy of Pediatrics. Lyme disease. In: Kimberlin DW, Brady MT, Jackson MA, Long SS, eds. *Red Book: 2015 Report of the Committee on Infectious Diseases.* 30th ed. Elk Grove Village, IL: American Academy of Pediatrics; 2015:516–525.

- Prophylaxis can be started within 72 hours of tick removal.
- Local rates of tick infection by *B burgdorferi* exceed 20%.
- The use of doxycycline is not contraindicated.
  - Doxycycline is the *only* antibiotic shown to be effective for postexposure prophylaxis.
  - A single 200-mg dose (4.4 mg/kg for body weight <45 kg) for people ≥8 years.
- No data are available to support amoxicillin use in this setting.

WHEN TO ADMIT

- Cardiac involvement
- Meningitis or encephalopathy

WHEN TO REFER

- Cardiac involvement (heart block, pericarditis, myocarditis)
- Neurologic involvement (except isolated facial palsy in patient with definite Lyme disease diagnosis)
- Nonspecific clinical history but positive or equivocal laboratory testing results
- Persistent arthritis

FOLLOW-UP

- None necessary if symptoms completely resolve with appropriate treatment

COMPLICATIONS

- Chronic pauciarticular arthritis
- Heart block
- Meningitis
- Cranial neuropathy
- Radiculopathy
- Posttreatment Lyme disease
  - Often referred to by the lay press as "chronic Lyme."
  - After antibiotic treatment, patients can have lingering symptoms of fatigue and muscle and joint aches.
  - In a very small percent, these symptoms can last for up to 6 months.
  - The cause of these lingering symptoms is unknown; it is thought to be autoimmune in nature.
  - Studies have not shown an improvement in symptoms with prolonged antibiotic use versus placebo.
  - Treatments similar to those in chronic fatigue and fibromyalgia have been found to be most effective.
  - Most symptoms resolve with time.

PREVENTION

- Ticks are most likely to be located in wooded and bushy areas with high grass, including forests, fields, and dunes.
- When walking in a tick-infested area, people should walk in the center of the path to avoid contact with grass and brush.

- Insect repellent containing *N,N*-diethyltoluamide (DEET) should be applied to skin and clothing.
  - DEET-containing compounds can be used for infants and children >2 months, should not be applied to the face or hands, and should be removed from skin with soap and water once the risk of exposure is over.
  - Permethrin kills ticks on contact and can be applied to clothing but should not be applied directly to skin because it is inactivated by skin lipids.
- Long pants and sleeves will help keep ticks off skin.
- Light-colored clothing makes the task of spotting ticks easier.
- Daily tick checks should be performed, paying particular attention to hairline, creases, and waistbands/bra lines.
- If a tick is attached for <24 hours, the risk of acquiring Lyme disease is extremely small.
- Attached ticks should be removed as soon as possible using fine-tip forceps.
- A vaccine is currently not available.
- See specific treatments for review of antibiotic prophylaxis.

Lymphadenopathy

DEFINITION

- Lymphadenopathy is defined as any lymph node enlargement.
- All lymph nodes that are palpable are technically considered to be enlarged but may not be clinically significant.
- Enlargement of ≥1 lymph nodes is a common finding in childhood.
  - Nodes in the cervical chain, occipital, and inguinal areas drain regions that are commonly infected in childhood.
  - These nodes often are mildly enlarged (<1 cm in diameter) in children who are otherwise healthy.

HISTORY

- Inquire about
  - Infectious exposures
  - Medications
  - Weight loss
  - Fever
  - Night sweats
  - Bone pain
  - Localized infection
    - Dental abscess
    - Mastoiditis
    - Scalp infection
    - Insect bite
    - Cat scratch
    - Pharyngitis
  - Systemic diseases
    - Infectious mononucleosis
    - Juvenile idiopathic arthritis
    - HIV

PHYSICAL EXAMINATION

- The physical examination should include all palpable nodes, as well as the tonsils, liver, and spleen.
- Determine whether any lymph node or lymph node aggregate or chain is abnormal and requires further assessment.
- Abnormal lymph node: enlarged, tender, warm to touch, fluctuant, fixed to skin or underlying structures.
  - Any abnormal node.
    - Determine whether the node is benign, primarily inflammatory, or malignant.
  - Fluctuance and signs of inflammation surrounding a group of enlarged lymph nodes
    - Strongly suggest an infectious cause, primarily bacterial.
    - Are helpful in reaching a diagnosis, particularly if an infectious source is found distal to the node area.
  - No inflammation, firm consistency, and nodes that are not mobile indicate possible cancer.
    - Lymphoma
    - Leukemia
    - Histiocytosis
    - Metastases from solid tumors (eg, neuroblastoma, Wilms tumor, Ewing sarcoma, rhabdomyosarcoma)
  - Hard, fixed nodes.
    - Seen more often in adults with metastatic carcinoma.
    - Nodes associated with neuroblastoma, rhabdomyosarcoma, and other childhood cancers may mimic this adult pattern.
  - Nodes that are more matted than hard indicative of
    - Hodgkin disease
    - Lymphoma

DIFFERENTIAL DIAGNOSIS

- **Table 1** lists diseases associated with lymphadenopathy.
- Anatomic location of mediastinal masses and associated conditions.
  - Anterior mediastinum
    - Lymphoma
    - Thymoma
    - Malignant germ cell tumor
    - Benign teratoma
    - Substernal goiter
    - Thymic hyperplasia
    - Thymic cyst
    - Mesenchymal tumors
  - Middle mediastinum
    - Lymphoma
    - Tuberculosis
    - Sarcoidosis
    - Histoplasmosis
    - Castleman disease
    - Bronchogenic cyst
    - Sarcoma
  - Posterior mediastinum
    - Neuroblastoma
    - Ganglioneuroma
    - Neurofibroma
    - Primitive neuroectodermal tumor
    - Sarcoma
    - Germ cell tumor
    - Schwannoma
    - Duplication cyst

Table 1. Entities Associated With Lymphadenopathy[a]

	Generalized	Cervical	Other Regional
Infections			
Viral			
Respiratory viruses (adenoviruses, picornaviruses, respiratory syncytial virus, parainfluenza, influenza, coronaviruses)		1–3+	
Epstein-Barr virus	2–3+	3+	+
Cytomegalovirus	2+	2+	
Primary human herpesvirus type 6		+	2–3+ (postoccipital)
Parvovirus B19	1–2+		2+
HIV	2–3+	+	+
Rubella	2+	3+	+
Rubeola	1–2+	3+	
Varicella zoster	1–2+	+	+
Herpes simplex virus		3+	1–2+ (genital infection)
Human herpesvirus type 8	2–3+	2–3+	+
Hepatitis A	+	2+	
Bacterial			
Staphylococcus aureus		3+	2–3+
Streptococcus pyogenes	+	3+	2–3+
Bartonella henselae (cat-scratch disease)	+		2–3+
Bartonella bacilliformis (Oroya fever, verruga peruana)	3+	3+	3+
Yersinia enterocolitica	+		3+
Salmonella typhi	2–3+		2+
Tularemia	+	3+	2+
Brucellosis	2–3+	+	+
Anaerobic			
Dental, gingival infections		2–3+	2–3+
Postanginal sepsis		2–3+	
Mycobacteria			
Mycobacterium tuberculosis	+	2–3+	2–3+
Atypical mycobacteria		2–3+	2–3+
Spirochetal			
Syphilis	2–3+	+	+
Lyme disease			+
Leptospirosis	3+	+	+

Table 1 (*continued*)

	Generalized	Cervical	Other Regional
Rickettsia/Chlamydia			
Lymphogranuloma venereum			3+
Ehrlichiosis	2–3+		
Rickettsia tsutsugamushi	3+	2–3+	3+
Protozoan			
Toxoplasmosis	+	3+	+
Malaria	+		
Parasitic **(Toxocara canis, Toxocara cati, Baylisascaris procyonis, Trichinella spiralis, Trichinella filariasis)**	1–2+	+	1–2+
Myiasis		+	1–2+
Fungal			
Histoplasmosis	1–3+	+	1–2+
Coccidiomycosis	1–3+	+	1–2+
Tinea capitis			2–3+
Immunizations			
Viral	+		+
Typhoid	+		+
Bacille Calmette-Guérin			1–3+
Neoplastic			
Leukemia	1–2+		
Lymphoma	1–3+	2–3+	2–3+
Hodgkin disease		2–3+	2–3+
Metastatic, solid tumors (neuroblastoma, Wilms tumor, Ewing sarcoma, rhabdo-myosarcoma)	1–2+		1–2+
Histiocytoses			
Langerhans cell histiocytosis		1–3+	
Malignant histiocytosis		1–2+	1–2+
Sinus histiocytosis (Rosai-Dorfman disease)		3+	
Hemophagocytic syndromes	1–2+	2+	
Immunologic			
Deficiency syndromes	1–2+	1–2+	2–3+
Autoimmune lymphoproliferative syndrome	2–3+		
Serum sickness	2+	+	+

Table 1 (*continued*)

	Generalized	Cervical	Other Regional
Immunologic (*continued*)			
Omenn syndrome	1–2+	+	+
Juvenile idiopathic arthritis	1–2+	+	+
Atopic disease, eczema	2–3+	2+	2–3+
Castleman disease	1–3+	3+	2–3+
Medications (phenytoin and others)	1–2+		
Storage diseases (Gaucher disease, Niemann-Pick disease)	2–3+		1–3+
Granulocyte Defects			
Chronic granulomatous disease	+	1–2+	2–3+
Leukocyte adhesion deficiencies		1–3+	1–3+
Chédiak-Higashi syndrome		1–3+	1–3+
Other			
Kawasaki disease		2–3+	
Hemoglobinopathy conditions	+	1–2+	
Hemophilia with HIV	2–3+	+	+
Sarcoidosis	2–3+	+	1–2+
Gianotti-Crosti syndrome	3+	+	+
Necrotizing lymphadenitis (Kikuchi-Fujimoto disease)	+	2–3+	2–3+
Insect bites		+	+
Kimura disease		2–3+	1–2+
Addison disease	1–2+		
Hyperthyroidism	1–3+		

[a] Numbers represent relative prominence and incidence of lymphadenopathy.

- For hilar or mediastinal adenopathy
  - Assess promptly for neoplastic or granulomatous causes.

LABORATORY EVALUATION

- Complete blood cell count
  - Reactive lymphocytes
    - Infectious mononucleosis
  - Granulocytosis with a shift to the left
    - Systemic bacterial infection
  - Bicytopenia (eg, anemia, granulocytopenia, thrombocytopenia)
    - Hematologic cancer, such as leukemia or lymphoma
    - Metastatic disease involving the bone marrow, such as neuroblastoma
  - Nucleated erythrocytes and immature granulocytes (leukoerythroblastic blood picture) on the blood film
    - Bone marrow irritation, with premature release of blood cell precursors
    - Metastatic diseases
      - Neuroblastoma
      - Rhabdomyosarcoma
    - Immunologic vasculitis
    - Granulomas (mycobacteria) in the marrow

- Isolated leukopenia and neutropenia
  - — Viral infections
  - — Severe bacterial infections (particularly in infants)
- Acute phase reactants: C-reactive protein, erythrocyte sedimentation rate
  - May reflect infection, vasculitis, or neoplasm
- When infection is suspected, helpful studies may include
  - Serologic assessment
  - Antigen detection
  - Polymerase chain reaction
  - Anaerobic and aerobic culture of material obtained from biopsy or aspiration
    - — Including routine staining and special staining (eg, Warthin-Starry silver stain for cat-scratch disease)
- Purified protein derivative or interferon gamma release assay indicated
  - When tuberculosis is suspected

IMAGING

- Chest radiograph.
  - The sensitivity and specificity of methods to define chest (mediastinal or hilar) lymphadenopathy are variable.
  - In a study of patients thought to have tuberculosis, the chest radiograph was 67% sensitive and 59% specific compared with spiral chest computed tomography (CT) with contrast.
- A variety of imaging modalities may be used, including ultrasonography, CT, magnetic resonance imaging (MRI), nucleotide or positron emission tomographic scanning, and scintigraphy.
- Specific regions studied include
  - Abdomen
    - — Retroperitoneal, periportal, and celiac nodes
    - — Nodes of the splenic hilum
  - Spleen
    - — Ultrasonography or CT
  - Abdominal and pelvic lymph nodes
    - — Ultrasonography, CT, MRI

DIAGNOSTIC PROCEDURES

- Biopsy.
  - Should be performed at a medical center that specializes in the care of children.
  - For significantly enlarged, unexplained adenopathy
    - — If no evidence of infection or other cause exists
    - — If mediastinal or hilar nodes are enlarged
  - Biopsy sample should encompass the central mass of the enlarged nodes to avoid misdiagnosis of reactive inflammation in adjacent nodes.
  - For suspicion of tuberculosis
    - — Needle aspiration should be avoided to prevent spread of infection and creating a track.
    - — Excisional biopsy is required.
    - — Even in the absence of mediastinal or hilar adenopathy.
    - — Allows initiation of appropriate therapy.
- Fine-needle aspiration biopsy.
  - Reserved for surgically inaccessible nodes; not recommended for biopsy of superficial, accessible nodes.
  - May be useful for intrathoracic nodes to avoid thoracotomy.
  - Acute cervical adenitis.
    - — Acutely inflamed, sometimes fluctuant, node demonstrates the infecting organism in two-thirds or more of cases.
  - Negative findings are not definitive.
- The pathology of Hodgkin disease, lymphoma, and other similar round-cell tumors may be difficult to establish.
  - Requires the assessment of a pediatric pathologist who has experience in these diseases
- Precise diagnosis may require
  - Immunophenotyping
  - Cytogenetic analysis
  - Molecular studies of gene rearrangement
  - Electron microscopy

TREATMENT APPROACH

- If a bacterial source for localized adenopathy (eg, pharyngitis, cervical nodes) is suggested, a limited course of 7–10 days of antibiotic therapy may be tried.
- Further evaluation should be carried out promptly, if the nodes have not regressed significantly after the trial.
- Treatment of neoplastic causes is, in most instances, oriented toward cure.

SPECIFIC TREATMENT

Infectious Disease

- Therapy for lymphadenitis depends on the cause or most likely cause.
- Infection with group A β-hemolytic streptococci or *Staphylococcus aureus.*
  - In children beyond the neonatal period who have acute localized adenitis, particularly cervical adenitis.

  - Antibiotics directed at group A streptococci and penicillinase-producing strains of *S aureus*
- Community-acquired methicillin-resistant *S aureus.*
  - Treatment should include an antibiotic to cover methicillin-resistant *S aureus.*
- For most patients, oral therapy is adequate.
  - Typical length of treatment is 10–14 days.
  - Treatment should be continued for ≥5 days after signs of acute inflammation have subsided.
- For patients who have suppurative adenitis from these organisms, drainage is not only diagnostic (by culturing the exudate) but also therapeutic.
- Parenteral antibiotic therapy is required in patients who do not respond to oral therapy.
  - Even with a drug to which the organism is sensitive

- Anaerobic infection.
  - Therapy depends on location of the adenitis and type of organism.
  - Most anaerobic infections of the cervical and submental areas are associated with mouth flora; most are sensitive to penicillin.
  - Alternative therapy.
    - Clindamycin
    - Amoxicillin-clavulanate
    - Metronidazole
    - Some cephalosporins
- *Mycobacterium tuberculosis* and atypical mycobacteria may be difficult to differentiate.
  - Many strains of atypical mycobacteria are resistant to the usual antitubercular chemotherapy.
  - If tubercular infection is suspected, excisional biopsy may be required.
  - Appropriate therapy for *M tuberculosis* should be initiated while awaiting identification and sensitivities of the organism.
    - Adenitis that is thought to be tubercular should not be incised or drained.
- Cat-scratch disease (*Bartonella* species, especially *B henselae*) is usually self-limited.
  - Some antibiotics, alone or combined, may be of clinical benefit.
    - Azithromycin
    - Erythromycin
    - Rifampin
    - Trimethoprim-sulfamethoxazole
    - Doxycycline
    - Parenteral aminoglycosides
- For markedly enlarged, tender, and fluctuant nodes
  - Aspiration may help relieve symptoms.
  - Incision and drainage should be avoided.
- For severe primary herpes simplex infection with localized adenitis (unusual)
  - Treatment with oral acyclovir to shorten the clinical course

Neoplastic Disease

- Effectiveness of therapy is markedly improved for
  - Lymphocytic and myelocytic leukemia
  - Lymphomas
  - Wilms and other tumors

WHEN TO REFER

- History and physical examination do not suggest an infectious cause.
- Potentially infectious nodes have not responded to a course of antibiotics.
- Mediastinal or hilar adenopathy is present.
- When biopsy is considered.
  - Biopsies should be performed only at a center specializing in the care of children.

WHEN TO ADMIT

- When biopsy requires hospitalization (mediastinal or hilar biopsy)
- When biopsy results require inpatient treatment or further evaluation
- When an infection requires intravenous therapy

Macrocephaly

DEFINITION

- *Macrocephaly* is defined as a head circumference >2 standard deviations (SDs) above the mean (~97th percentile) based on age and sex.

HISTORY

- Review previously measured head circumferences.
  - Determine whether a child has had any change in pattern or percentiles of head circumferences over time.
- A large head circumference at birth
  - Presupposes a cause of prenatal origin
  - Necessitates a detailed prenatal history
  - May indicate anatomic megalencephaly
  - Conditions that may cause congenital macrocephaly
    - X-linked aqueductal stenosis
    - Overgrowth syndromes
- An abnormally enlarging head postnatally in a child with neurodevelopmental problems is a clue to an acquired condition, such as
  - Acquired hydrocephalus.
  - A possible metabolic disorder.
  - History should explore
    - Delays in developmental milestones
    - Regression in motor, language, and social skills
    - Seizures
    - Signs of increased intracranial pressure
      - Lethargy
      - Vomiting
      - Behavioral changes
  - A family history of any genetic, neurologic, and developmental condition may be a red flag for similar disorders.
- Online Mendelian Inheritance in Man is a comprehensive list of syndromes associated with macrocephaly and megalencephaly.
- A history of otherwise typical parents and siblings with large heads can be reassuring.

PHYSICAL EXAMINATION

- Physical examination of the child with macrocephaly should focus on
  - Accurate measurement of the head circumference and assessment of the pattern of head growth
  - Inspection and palpation of the skull
  - Comparison of the head circumference with other growth parameters
  - Presence or absence of dysmorphic features
  - Presence or absence of congenital abnormalities involving other organ systems
  - Thorough neurologic and developmental assessment, including a check for signs of increased intracranial pressure
  - Skin examination with Wood lamp
- Monitoring of head size must be performed periodically during health care maintenance visits.
  - In the presence of a rapid enlargement in head circumference, more frequent monitoring is necessary.
  - Measurements should be plotted on the appropriate head circumference charts.
  - A disproportionately enlarged head relative to height and weight may indicate a primary neurologic disorder.
  - Measuring the size of the fontanels and palpating sutures are important.
    - Significant hydrocephalus in infants may produce a bulging anterior fontanel and separation of cranial sutures, which are uncommon in anatomic megalencephaly.
  - A Galen vein arteriovenous malformation may produce a cranial bruit on auscultation.
  - Because macrocephaly is a feature of many genetic syndromes, dysmorphic features and other organ involvement should be noted.
  - Examination of the skin may reveal
    - Café au lait spots
    - Axillary freckling
    - Ash leaf macules
    - A whorled pattern of pigmentation that may indicate a neurocutaneous disorder
  - Careful neurologic examination is critical and may reveal
    - Abnormalities in muscle tone and posture
    - Asymmetries
    - Persistence of primitive reflexes
    - Hyperreflexia
- Developmental assessment may reveal
  - Cognitive impairment
  - Autistic features
  - Learning disabilities
  - Behavioral difficulties
- Measure head circumference of the parents and note any dysmorphic features.

DIFFERENTIAL DIAGNOSIS

Hydrocephalus

- Enlargement of the ventricular system
- May be congenital or acquired
- Clinical presentation is influenced by
  - Age of onset
  - Underlying condition causing the hydrocephalus

- Infants
  - Enlarging head circumference is the most obvious finding because cranial sutures have not fused.
- In older children whose sutures have fused
  - Significant head enlargement does not occur.
  - Other signs and symptoms of increased intracranial pressure may occur.
    - Headaches
    - Vomiting
    - Papilledema
- Hydrocephalus with intraventricular hemorrhage
  - Intraventricular hemorrhage occurs in ~15% of preterm neonates with birth weight <1,500 g.
  - Although subtle changes in head circumference may be present, macrocephaly is not always evident in neonates with intraventricular hemorrhage.
  - Grade III and IV hemorrhages are associated with poorer neurodevelopmental outcomes than grade I and II hemorrhages.
    - An estimated 35% and 90% of affected children, respectively, show neurologic sequelae.
- Hydrocephalus with Chiari type II malformation
  - Present in 80% of children with myelomeningocele
- Dandy-Walker malformation
  - Cystic dilatation of the fourth ventricle with
    - Macrocephaly—commonly the first manifestation
    - Hypoplasia of the cerebellar vermis
    - Various other cranial malformations
  - Head size may be normal at birth, but acceleration in head growth is noted in most children by 1 year.
    - Sometimes shows prominence of the posterior part of the skull
- Congenital aqueductal stenosis
  - May occur sporadically or be transmitted by X-linked inheritance
  - Severe hydrocephalus may
    - Complicate labor and delivery with cephalopelvic disproportion
    - Lead to signs and symptoms of increased intracranial pressure after birth
- Benign accumulation of extracranial fluid, probably subarachnoid
  - May be seen in many children with macrocephaly who have an unremarkable neurologic examination.
  - The exact nature of fluid collection is not clearly established and is variously called
    - Benign macrocephaly
    - External hydrocephalus
    - Benign extracerebral fluid collections
    - Benign subdural collections
    - Benign enlargement of the subarachnoid space
  - Fluid collection is most evident in the prefrontal area.
  - In some cases, there is mild nonprogressive dilation of the ventricular system.
  - Brain size is normal.
  - Normal or large head circumferences at birth.
  - In succeeding months, head circumference grows to >98th percentile and then generally parallels the normal growth curves.
  - Large head size is an isolated feature; the affected child has an otherwise normal neurologic examination and age-appropriate development.
    - Transient early developmental delays may be seen, especially in the first year after birth.
  - Condition appears to be self-limited, with normalization of computed tomography (CT) findings usually by 2.5 years of age.
  - Relationship to benign megalencephaly has not been established and is not fully understood.
  - Association with subdural hematoma in infancy has been suggested.

Megalencephaly

- Benign or idiopathic megalencephaly
  - Large head.
  - No significant collection of extraventricular or intraventricular fluid.
  - Normal neurologic examination and developmental history.
  - No signs of increased intracranial pressure.
  - Family history of large head sizes in typical adult megalencephaly.
  - Although these individuals have been thought to develop normally, recent evidence suggests they may exhibit mild neurodevelopmental dysfunction, such as incoordination and visual-motor weaknesses.
- Anatomic megalencephaly
  - Usually associated with neurodevelopmental impairment.
  - The brain is abnormally large because of an increase in the size and number of its cells.
  - Overgrowth syndromes.
    - Generalized increase in body size with macrocephaly; usually present at birth

- Cerebral gigantism (Sotos syndrome)
  - Facial dysmorphism.
  - Neurodevelopmental deficits, such as poor coordination and cognitive and behavioral problems.
  - Macrocephaly may result from a combination of
    - Megalencephaly
    - Ventricular enlargement
    - Midline anomalies
    - About 90% of clinical cases have mutations or deletions involving the *NSD1* gene in chromosome 5q35.
- Neurocutaneous syndromes, such as
  - Neurofibromatosis
  - Tuberous sclerosis
  - Hypomelanosis of Ito
  - Associated with megalencephaly in addition to characteristic skin findings, intracranial conditions, and neurodevelopmental problems
- Achondroplasia.
  - Megalencephaly
  - Short stature
  - Shortened proximal arms and legs (rhizomelia)
  - Dysmorphic facial features
  - Normal intelligence
  - Risk for
    - Hydrocephalus
    - Obstructive sleep apnea
    - Central apnea
    - Spine and joint problems
- Autism spectrum disorder (ASD).
  - Compared with the general population, a disproportionate number of children with ASD have enlarged heads.
    - The pattern of brain growth in some children with ASD appears to be abnormal, with
      - Acceleration of head growth in early childhood
      - Hyperplasia in cerebral gray matter and cerebral and cerebellar white matter
      - Slight decrease in brain volume during adolescence
  - The relationship between acceleration in head growth and behavioral and developmental regression remains unclear.
- Fragile X syndrome.
  - Macrocephaly
  - Longish face with prominent ears
  - Joint hyperextensibility
  - Enlarged testes
  - Family history on the mother's side of
    - Intellectual disability
    - Developmental and behavioral problems
    - Autistic behaviors
- Metabolic megalencephaly
  - Mucopolysaccharidoses (MP)
    - Hurler syndrome—the most severe MP
      - Enlarging head that quickly crosses percentiles during infancy
      - Coarse facial features
      - Frontal bossing
      - Corneal clouding
  - Leukodystrophies
    - Infantile form of Canavan disease
      - Irritability
      - Poor visual fixation
      - Head lag
      - Motor delay
    - Alexander disease
      - Macroencephaly
      - Spasticity
      - Seizures
      - Developmental regression
  - Glutaric aciduria

Thickening of the Skull

- Hemolytic anemia (eg, β-thalassemia)
  - May exhibit frontal bossing attributable to extracranial hematopoiesis of skull bones
- Cleidocranial dysostosis
  - Autosomal-dominant disorder of abnormal bone formation characterized by
    - Delayed closure of fontanels
    - Widening of the head circumference
    - Other skeletal abnormalities

Space-Occupying Lesions

- Arteriovenous malformation.
- Brain tumors.
- Subdural effusion as a complication of bacterial meningitis in infants may produce
  - Enlarging head circumference
  - Bulging anterior fontanel
  - Signs of increased intracranial pressure
- Subdural hematoma may present with macrocephaly in infants but is usually associated with other symptoms.

LABORATORY EVALUATION

- Metabolic testing
  - Available to identify many of the storage diseases
  - Recommended in a child exhibiting developmental regression
- Genetic testing as appropriate for clinical assessment

IMAGING

- Neuroimaging
  - Procedure of choice in evaluating macrocephaly
  - Magnetic resonance imaging
    - Most informative
    - Good for identifying
      - Gray and white matter disease (eg, leukodystrophy)
      - Migration defects
      - Hydrocephalus
      - Posterior fossa lesions
      - Subtleties in subdural and subarachnoid hemorrhage
    - Generally not indicated in patients with ASD and macrocephaly unless there are concerns not explained by ASD
  - CT
    - Can identify
      - Hydrocephalus
      - Intracranial calcifications
      - Hemorrhages
  - Head ultrasonography
    - For infants with open fontanels, useful in identifying
      - Intraventricular hemorrhage
      - Hydrocephalus
      - Intracranial tumors
- Skeletal survey
  - May reveal
    - Bone age abnormalities in the overgrowth syndromes
    - Abnormalities that may be present in MP
    - Bone dysplasias
    - Trauma

TREATMENT APPROACH

- Management of macrocephaly depends on its cause.

SPECIFIC TREATMENT

Hydrocephalus

- Shunting is the treatment of choice for significant and progressive hydrocephalus.
  - Complications are not rare and continue to be challenging in the care of these children, owing to
    - Infection
    - Obstruction
    - Malfunction
  - Risks are even greater in preterm neonates, asymptomatic, or mildly symptomatic patients.
  - With Dandy-Walker cysts, dual shunting has been recommended to drain the hydrocephalus and posterior fossa cyst.
- Lumbar puncture.
  - Serial lumbar punctures may be used as initial therapy.
- Medical management.
  - Carbonic anhydrase inhibitors
  - Other diuretics

Other

- Children suspected to have inborn errors of metabolism.
  - Should be referred for genetic evaluation, treatment, and counseling.
  - Treatment for these conditions is mainly supportive and symptomatic.
  - Bone marrow transplantation and enzyme replacement therapy are promising interventions for certain disorders.
- Anatomic megalencephaly.
  - The association with developmental and cognitive problems warrants early intervention and special education services.
- Subdural hematoma requires further evaluation.
  - Skeletal survey, retinal examination
- Benign accumulation of extracranial fluid and idiopathic megalencephaly.
  - Serial measurement of the head circumference
  - Ongoing clinical assessments

WHEN TO REFER

- Head circumference >2 SDs above the mean
- Head circumference that is crossing percentiles or growing rapidly
- Dysmorphic features
- Abnormal neurologic examination
- Regression in developmental skills or significant developmental delay
- Suspected child abuse

WHEN TO ADMIT

- Signs of increased intracranial pressure or mental status change
- Shunt infection or malfunction

DEFINITION

- *Meningitis,* or inflammation of the meninges, is most often caused by an infectious agent and less commonly by a chemical (medication) or cancer.
- Bacterial meningitis, also known as *pyogenic meningitis,* is often quickly fatal, making early diagnosis and treatment essential.
- *Aseptic meningitis* refers to inflammation of the meninges without the presence of visible microorganisms on routine Gram staining.
  - Not synonymous with *viral meningitis,* although the 2 terms are often used interchangeably.
- Neonatal meningitis is considered separately because
  - Agents that cause it are unique.
  - It is more often fatal than meningitis in the older child.

SIGNS AND SYMPTOMS

Bacterial Meningitis

- Fever is usually present in bacterial meningitis.
- Absence of fever in a child with signs of meningeal irritation does not preclude the diagnosis.
- Inflammation of the meninges can be characterized by
  - Irritability
  - Anorexia
  - Headache
  - Nausea
  - Vomiting
  - Confusion
  - Back pain
  - Nuchal rigidity
  - Photophobia
- The Kernig and Brudzinski signs can be assessed during physical examination to demonstrate meningeal inflammation.
  - Kernig sign
    - Extend the leg at the knee of the supine patient while the hip is flexed at 90°.
    - When positive result, the maneuver causes extensor spasm of the knee and pain in hamstrings when the lower leg is extended to ~135°.
  - Brudzinski sign
    - Flex the neck of the patient in the supine position.
    - When positive result, the patient will involuntarily flex hips and knee.
    - Stiffness of neck is a sensitive (80%–98%) indicator of true bacterial meningitis in children, adolescents, and adults.
- In a young infant, signs of meningeal inflammation can be minimal or absent.
  - In patients <12 months, absence of nuchal rigidity must not be used to exclude meningitis.
  - Distinguishing nuchal rigidity from voluntary movement and guarding can be difficult in a sick infant with irritability.
    - Additional signs may be helpful: lethargy, poor feeding, restlessness.
  - Lay the infant near the edge of the examining table, with the head supported by the examiner's hand but gently extended off edge of table.
    - The natural tendency for an infant in this position will be to try to lift the head.
    - The examiner can feel whether nuchal rigidity is preventing flexion of the neck rather than voluntary guarding or noncooperation.
- Signs and symptoms of increased intracranial pressure may be seen.
  - Headache
  - Bulging fontanel
- Papilledema is uncommon.
  - When present, other causes should be sought.
  - Bacterial meningitis progresses so quickly that the time needed for papilledema to develop may not be sufficient.
- Cranial nerve involvement occurs with bacterial meningitis; although often transient, it can be permanent.
- The auditory nerve is often affected.
  - Deafness
  - Disturbances of vestibular function
- Blindness is rare but has been reported.
- Children may have paralysis of extraocular or facial nerves.
- The degree of central nervous system (CNS) derangement observed with bacterial meningitis ranges from irritability to coma.
  - ~15% of children with bacterial meningitis are comatose or semicomatose at the time of hospitalization.
    - Occurs more often with *Streptococcus pneumoniae* or *Neisseria meningitidis* than with *Haemophilus influenzae* type b (Hib).
  - Seizures occur before or within 1–2 days after admission in ~30% of patients.
  - Focal neurologic signs correlate with persistent abnormal neurologic and developmental examinations 1 year after discharge in ~16% of patients.

- Distinction from infectious meningoencephalitis may be difficult when the child with coma or seizures first presents.
- Subdural effusions occur in ~50% of children with bacterial meningitis.
  - Seldom clinically significant.
  - Effusions need not be sought through subdural taps or computed tomography (CT) unless focal neurologic signs or signs of increased intracranial pressure develop.
  - Infection of subdural effusions is extremely rare.
- Arthralgia and myalgia often occur, particularly in those with meningococcemia.
- Vasculitis can be seen in children with any type of bacterial meningitis.
  - Petechiae and purpura are more commonly associated with meningococcal disease.
  - Children who have such rashes should be considered in imminent danger of developing septic shock.
- Clinical signs associated with neonatal meningitis are nonspecific.
  - Neonates with meningitis often have apneic episodes or feed poorly, and they can exhibit
    - Hyperthermia or hypothermia
    - Irritability or lethargy
    - Respiratory distress or diarrhea (or both)
    - Nuchal rigidity (rarely)
    - Bulging fontanel
- The neonate has a limited repertoire of clinical responses to disease or insult.
  - Most sick neonates receive a diagnostic evaluation for sepsis, including lumbar puncture, and antimicrobial agents are initiated pending culture results.
- Cytology and chemistry of the cerebrospinal fluid (CSF) in neonates have a much broader reference range than children in other age groups, especially during the first week of life.
  - Any single test result may not appear abnormal.
  - Neonates with bacterial meningitis rarely have completely normal CSF at examination.
  - During the first 24 hours of life, isolated meningitis without sepsis occurs rarely enough that lumbar puncture has sometimes been omitted for neonates appearing septic on day of birth.
    - May lead to missed cases of early-onset or late-onset meningitis.
    - As many as 25% of neonates with meningitis have been found to have sterile blood cultures despite positive CSF culture results.
    - The proportion of such cases might increase as antibiotic prophylaxis is given to mothers and babies in the peripartum period.
    - If possible, any neonate thought to have sepsis or meningitis should undergo lumbar puncture.

Tuberculous Meningitis

- Often has an insidious onset with nonspecific symptoms for >1 week, including fever, vomiting, malaise, poor weight gain or weight loss, and decreased mentation.
- CSF profile tends to show lymphocytic pleocytosis, with a low glucose level and a moderate to markedly high protein level.
- Mantoux skin test result was positive in 60% of children with tuberculous meningitis in a large South African study.
  - It might be positive more often in areas with fewer nutritional deficits.
- Tuberculosis of the CNS most often presents as basilar meningitis, but parenchymal tuberculoma and hydrocephalus may also be seen.

Aseptic Meningitis

- Infants and children who have aseptic meningitis caused by enteroviruses may exhibit
  - Acute fever
    - Usually 38.0°C–40.5°C (100.4°F–105.0°F) for 4–5 days
  - Irritability
  - Lethargy
  - Upper respiratory tract symptoms
  - Headache
  - Photophobia
  - Nausea
  - Vomiting
  - Rashes
- Aseptic meningitis is likely when
  - CSF pleocytosis ranges from 10–500 cells/mcL that are predominantly lymphocytes.
  - CSF protein level is mildly high, at 50–150 mg/dL.
  - CSF glucose concentration is within reference range.

Viral Meningitis

- In general, a child with viral meningitis does not appear as critically ill as a child with bacterial meningitis.
  - Less likely to have meningeal signs

- Early in the course of viral meningitis, polymorphonuclear neutrophils can predominate in the CSF.
  - Transition from predominance of polymorphonuclear neutrophils to lymphocytes usually occurs rapidly.
  - Repeat lumbar puncture after 8–12 hours may show transition.
- Tuberculous and fungal meningitis generally have gradual onset of illness over days to weeks.
- Hypoglycorrhachia (low CSF glucose level) rarely occurs with viral meningitis caused by
  - Enteroviruses, mumps
  - Herpes simplex
  - Eastern equine encephalitis viruses
  - Hypoglycorrhachia caused by these viruses tends to result in CSF glucose concentrations that equal ~30% of simultaneous blood glucose concentration.
    - Bacterial meningitis usually results in CSF glucose concentrations <30% of blood glucose.
    - CSF glucose concentration can also be low with tuberculous and fungal meningitis.
- For a long time, many physicians were reluctant to obtain specimens for viral culture because they thought that isolating viruses took too long to affect management, and polymerase chain reaction (PCR) is a reliable, rapid alternative.
  - Diagnosis of enteroviral meningitis frequently results in discontinuation of antimicrobial therapy and early discharge from the hospital.
  - Therefore, when viral meningitis is a possibility, viral cultures of the CSF, nasopharyngeal or throat, and rectal swab should be considered.
  - Isolation of a virus from a site other than CSF can be misleading.
    - Taken in the context of other clinical and laboratory findings, a presumptive diagnosis often can be made when virus is isolated from ≥1 sites.
- PCR is a rapid and sensitive method of diagnosing meningitis caused by
  - Enteroviruses
  - Herpesviruses
  - Possibly other viruses
- PCR amplification of enteroviral RNA from CSF and serum appears to have good sensitivity, specificity, and predictive value.
  - Where PCR for enterovirus is available, it may substitute for viral culture in many cases.

DIFFERENTIAL DIAGNOSIS

- Signs and symptoms suggesting meningeal inflammation or increased intracranial pressure can be seen with other CNS infections.
  - The most common cause of meningeal inflammation is enteroviral aseptic meningitis.
- **Table 1** lists selected causes of aseptic meningitis.
- Meningitis or meningoencephalitis may also be present in patients with
  - Rocky Mountain spotted fever
  - Kawasaki disease
  - Cat-scratch disease
  - Toxic shock syndrome
- Meningitis often is associated with or occurs after
  - Mumps
  - Rubeola
  - Rubella
  - Varicella
  - Infectious mononucleosis
  - Roseola
  - Erythema infectiosum
- The following conditions can mimic bacterial meningitis:
  - Brain abscess
  - Epidural abscess
  - Primary amebic meningoencephalitis
  - Embolic diseases (eg, endocarditis, thrombophlebitis)
  - Venous sinus thrombosis
  - Space-occupying lesions
  - Reactions to medications
    - Intravenous (IV) immunoglobulin (IVIG)
    - IV monoclonal antilymphocyte antibody
    - Oral trimethoprim-sulfamethoxazole
    - Some oral nonsteroidal anti-inflammatory drugs
  - Ingestion of toxins (eg, lead)
  - Spider bites
  - Pemphigus
  - Behçet syndrome
- Eosinophilic meningitis is rarely seen; the differential diagnosis includes reactions to
  - Ventriculoperitoneal shunts
  - Unusual presentations of bacterial or *Toxoplasma* infection
  - Parasitic roundworms
- Conditions that can simulate a clinical picture of meningitis but that usually have normal CSF findings include
  - Pharyngitis
  - Retropharyngeal abscess

Table 1. Selected Causes of Aseptic Meningitis

Cause	Common[a]	Uncommon[a]	Rare[a]
Viruses	Enteroviruses Arboviruses Herpes simplex type 2 Human herpesvirus 6	HIV-1 Epstein-Barr virus Lymphocytic chorio-meningitis virus Mumps	Adenovirus Varicella-zoster virus Cytomegalovirus Measles Rubella Parvovirus B19 Influenza A and B
Bacteria	Pyogenic (partially treated) *Mycobacterium tuberculosis* *Borrelia burgdorferi* *Mycoplasma pneumoniae* *Leptospira* species	*Treponema palladium* *Borrelia* species *Bartonella henselae* *Rickettsia rickettsii* *Ehrlichia canis*	*Chlamydophila psittaci* *Chlamydophila pneumoniae* *Rickettsia prowazekii* *Coxiella burnetii* *Brucella abortus* *Streptobacillus moniliformis*
Fungi	*Candida* species *Cryptococcus neoformans* *Histoplasma capsulatum* *Coccidioides immitis*	*Blastomyces dermatitidis*	Various molds
Parasites	–	*Toxoplasma gondii* Neurocysticercosis	*Angiostrongylus cantonensis* *Baylisascaris procyonis* *Strongyloides stercoralis* Free-living amoebae
Miscellaneous	Parameningeal infections Kawasaki disease Foreign bodies (CSF shunts) CNS leukemia, tumors ADEM	Medications (TMP-SMX, IVIG, ibuprofen) Systemic lupus erythematosus	Sarcoidosis Behçet syndrome Heavy metal poisoning

Abbreviations: ADEM, acute disseminated encephalomyelitis; CNS, central nervous system; CSF, cerebrospinal fluid; HIV, human immunodeficiency virus; IVIG, intravenous immunoglobulin; TMP-SMX, trimethoprim-sulfamethoxazole.

[a] *Common, uncommon,* and *rare* refer to relative frequencies within each broad category of etiologic agents (eg, viruses, bacteria). Overall, enteroviruses cause at least 85% of the aseptic meningitis diagnosed in children in the United States, and arboviruses cause ~5%; all other causes combined account for the remaining ≤10% of cases.

- Cervical adenitis
- Cervical spine arthritis or osteomyelitis
- Pyelonephritis
- Pneumonia
- Torticollis
- Tetanus
- Oculogyric crisis

- Syndrome of aseptic meningitis consists of a clinical picture of meningitis with CSF pleocytosis and absence of bacteria on Gram stain or culture.
  - Aseptic meningitis is usually caused by a virus; treatable causes should be considered in the differential diagnosis.
  - Mumps and poliovirus should be considered in areas of the world where they are still endemic.
  - Longer duration of symptoms has been associated with Lyme disease meningitis, especially if accompanied by erythema migrans or cranial neuropathies.
- West Nile virus infection may cause
  - Aseptic meningitis
  - Meningoencephalitis
  - Acute flaccid paralysis

DIAGNOSTIC APPROACH

- The clinical situation should influence the amount of data required before a therapeutic decision is made.
- Interpretation of CSF findings in context of clinical manifestations usually differentiates bacterial meningitis from other diseases.
  - If CSF from an ill, febrile child is turbid or purulent, antimicrobial therapy for bacterial meningitis should be initiated before further laboratory results are available.
- In partially treated meningitis, antibiotics have been provided before lumbar puncture is performed.
  - Renders Gram staining and bacterial culture less useful (because of the possibility of temporary bacterial sterilization)
- Distinguishing partially treated bacterial meningitis with false-negative CSF culture results from aseptic meningitis can be difficult.
  - Accompanying CSF laboratory studies may be of assistance.
    - Leukocyte count and differential
    - CSF protein and glucose concentrations
- Reasons for delaying lumbar puncture include
  - Clinically important cardiorespiratory compromise, most often observed in the neonate
  - Signs of significantly increased intracranial pressure
    - Retinal changes
    - Altered pupillary responses
    - Increased blood pressure with associated bradycardia and hyperpnea (Cushing triad)
    - Focal neurologic signs during the physical examination
  - Infection in the skin, soft tissues, or epidural area at the site of lumbar puncture
  - Suspicion or history of bleeding disorders
    - Hemophilia
    - Severe thrombocytopenia
- In the previously listed circumstances, blood cultures should be obtained.
  - Antibiotics are provided empirically without performing a lumbar puncture.
  - In cases of suspected increased intracranial pressure
    - Arrangements should be made for cranial CT with and without contrast enhancement during or immediately after antibiotic administration.
    - If imaging suggests that it would be safe to proceed, lumbar puncture may follow.
    - Performing CT routinely before lumbar puncture is not necessary in patients with suspected meningitis.

LABORATORY FINDINGS

General Tests

- The initial laboratory examination should include
  - CSF examination and culture
  - Blood culture
  - Measurement of serum electrolyte and glucose concentrations
  - Complete blood cell and platelet counts
  - Measurement of urine specific gravity
- If the patient has petechiae or purpura or is in shock, laboratory tests should include
  - Partial thromboplastin time
  - Prothrombin time
  - Measurement of fibrinogen- or fibrin-breakdown products

CSF

- Most experts suggest that the following tests should be performed on CSF from all samples drawn by lumbar puncture:
  - Gram stain
  - Bacterial culture
  - Cell count

- Differential cell count
- CSF concentrations of total protein and glucose

- If the nucleated blood cell count of CSF is not >6/mcL, the only other tests likely to be useful in diagnosing bacterial meningitis are Gram stain and culture.
- If only a small amount of CSF is obtained, the most important tests to perform are Gram stain and bacterial culture.
- If possible, blood glucose should be measured just before lumbar puncture is performed to determine the ratio of CSF to blood glucose.
  - Measure the blood glucose level before lumbar puncture because stress of the procedure can temporarily increase it.
- CSF should be cultured on chocolate and blood agar plates and in broth.
  - Generally, bacterial cultures will be positive within 2 days if pathogens are present.
- The causative agent may be identified by latex agglutination reactions, immunochromatographic reactions, or PCR amplification of nucleic acids.
  - These tests are rapid but should not be viewed as essential; the negative predictive value does not approach 100%, and they are not that useful in directing patient care.
  - Rapid diagnostic tests are likely to be truly valuable only in patients who have received a significant amount of antibiotics ≥24 hours before lumbar puncture.
- Distinguishing CSF abnormalities caused by infection from those associated with traumatic lumbar puncture.
  - Common clinical practice is to use the ratio of erythrocytes to leukocytes to correct the observed CSF leukocyte count, either by subtraction or by examination of the ratio of observed to expected cells.
  - Despite this apparently sound theoretical basis, in practice, calculations are generally not helpful when deciding whether to proceed with antibiotic therapy.
  - Bacterial or viral cultures will yield a more definitive answer relatively quickly.
- **Tables 2** and **3** contain CSF findings.

Blood Cultures

- Blood cultures should be obtained for all children suspected of having bacterial meningitis.
  - Positive in 80%–90% of children who have not previously received antimicrobial agents and have meningitis caused by Hib, *S pneumoniae,* or *N meningitidis*

Partially Treated Meningitis

- Leukocyte counts in CSF, percentage of polymorphonuclear cells, and glucose and protein concentrations in patients with partially treated bacterial meningitis do not greatly differ from those in untreated patients.
- Even children who have received IV antibiotics for 44–68 hours have CSF findings still characteristic of bacterial meningitis.
- Cultures of CSF from pretreated children with bacterial meningitis frequently grow Hib.
  - Pneumococci and meningococci grow less often after pretreatment.
  - Some patients who have partially treated bacterial meningitis will have CSF findings indistinguishable from classic findings of aseptic meningitis.

IMAGING

- Obtaining CT before lumbar puncture in selected patients is reasonable, especially in children or adults with a history of
  - Immunosuppression
  - Hydrocephalus
  - Ventricular shunts
  - Head trauma
  - Focal neurologic signs
  - Signs of greatly increased intracranial pressure
- Radiographs may help in identifying suspected bone or joint infection in selected patients.
- Radionuclide and CT studies play a role in complicated cases.
  - May be helpful for decisions on management later during the course of therapy
  - Useful for evaluating selected cases of prolonged (primary) or recurrent (secondary) fever
- CT should not be routinely done as a result of prolonged or secondary fever; results are unlikely to affect clinical management.

DIAGNOSTIC PROCEDURES

- In general, lumbar puncture should be performed whenever the diagnosis of meningitis is known or suspected.
  - In children 6–12 months of age with a first febrile seizure a lumbar puncture is considered optional and is most important for those with signs of meningitis, pretreatment with antibiotics, or incomplete or unknown immunization histories.

Table 2. Characteristic Cerebrospinal Fluid Findings in Children With and Without Meningitis

CSF Findings	Normal	Bacterial	Viral	Fungal or Tuberculous
Leukocytes/mcL				
Usual	<5	>500	<500	50–750
Range	0–10	10–20,000	0–1,000	10–1,500
Polymorphonuclear Neutrophils (% of Leukocytes)				
Usual	2	>80	<50	<50
Range	0–20	20–100	0–100	0–80
Glucose, mg/dL				
Usual	60	<40	>40	<40
Range	45–65	0–65	30–65	5–50
Usual CSF/blood (%)	≥60	<30	30–60	<40
Protein, mg/dL				
Usual	≤30	>100	<100	50–200
Range	0–40	40–500	20–200	40–1,500
Other Positive Tests	None	Gram stain, antigen detection	Polymerase chain reaction	Cryptococcal antigen, acid-fast stain

Abbreviation: CSF, cerebrospinal fluid.

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Table 3. Representative Cerebrospinal Fluid Findings in Neonates Without Meningitis

CSF Finding	Full-term Neonates Mean (Range)		Preterm Neonates Mean (Range)	
	0–7 d	8–28 d	0–7 d	8–28 d
Leukocytes/mcL	8 (1–30)	6 (0–18)	4 (1–10)	7 (0–44)
Polymorphonuclear neutrophils (% of leukocytes)	5	3	7	9
Protein (mg/dL)	81	64	150 (85–222)	148 (54–370)
Glucose (mg/dL)	46	51	72 (4–96)	64 (33–217)
CSF/blood glucose (%)	0.73	0.62	Not reported	Not reported

Abbreviation: CSF, cerebrospinal fluid.

Data from Ahmed A, Hickey SM, Ehrett S, et al. Cerebrospinal fluid values in the term neonate. *Pediatr Infect Dis J*. 1996;15(4):298–303; Rodriguez AF, Kaplan SL, Mason EO Jr. Cerebrospinal fluid values in the very low birth weight infant. *J Pediatr*. 1990;116(6):971–974; Byington CL, Kendrick J, Sheng X. Normative cerebrospinal fluid profiles in febrile infants. *J Pediatr*. 2011;158(1):130–134; and Kestenbaum LA, Ebberson J, Zorc JJ, Hodinka RL, Shah SS. Defining cerebrospinal fluid white blood cell count reference values in neonates and young infants. *Pediatrics*. 2010;125(2):257–264.

- When meningitis is suspected in a patient without papilledema, lumbar puncture should be performed.
  - Opening pressure should be measured and the CSF examined immediately.
- Herniation of the brain associated with meningitis has been observed before lumbar puncture and in the presence of normal cranial CT.
  - Herniation of the brain on removal of a small amount of CSF is rare in meningitis, especially in infants with open fontanels.
  - Nevertheless, lumbar puncture should be performed cautiously if significantly increased intracranial pressure is suspected.
- If lumbar puncture was not initially performed or was contraindicated, the procedure may be reconsidered after
  - The patient has been stabilized.
  - Contraindications have been resolved.
- Lumbar puncture may be performed even 12–24 hours after initiation of antimicrobial therapy.
  - Interpretation of CSF leukocyte counts and protein and glucose concentrations may be helpful in discerning the likelihood of true bacterial meningitis.

TREATMENT APPROACH

- The severity of illness at the time the patient seeks care can predict morbidity and should dictate immediate management.
- Therapies that are crucial for all patients with bacterial meningitis include
  - Fluid management
  - Possible anti-inflammatory adjunctive treatments
  - Antimicrobial therapy
- Acute bacterial meningitis is always a medical emergency.
  - As soon as bacterial meningitis is diagnosed, IV administration of appropriate antimicrobial agents and, possibly, anti-inflammatory agents should begin.
- All infants and children with an altered state of consciousness should be observed closely and need for intensive care anticipated.
- Management of the child who is awake and has stable cardiorespiratory vital signs consists primarily of
  - Administering antimicrobial agents and fluids and careful monitoring for
    - Changes in level of consciousness
    - Development of seizures
    - Changes in vital signs
    - Development of the syndrome of inappropriate secretion of antidiuretic hormone (SIADH)
  - Other therapies should be considered in more critically ill children.
- Seizures should be treated with appropriate anticonvulsants.
  - An open airway that provides good oxygenation should be ensured.
- Patients who are in a profound coma or whose level of consciousness deteriorates while receiving therapy should be evaluated for complications.
  - Cerebral abscess.
  - Obstructive hydrocephalus.
  - Increased intracranial pressure.
  - CT of the brain with and without contrast is helpful in determining the diagnosis in such cases.
- If increased intracranial pressure is a major clinical concern and treatment has been initiated or is anticipated, a neurosurgeon should be consulted and an intracranial pressure monitoring device placed.
  - All children with bacterial meningitis have some increase in intracranial pressure.
  - Monitoring devices are not required for most patients.
  - If an intraventricular catheter can be placed, increased intracranial pressure can often be treated by removing CSF.
    - Placement of a pressure transducer affords continuous intracranial monitoring, so that mannitol and hyperventilation can be used as necessary to decrease pressure and maintain cerebral perfusion.
    - Decreased inflammation and increased cerebral perfusion probably account for the benefits reported by some investigators with dexamethasone therapy.

SPECIFIC TREATMENTS

Fluid Therapy

- Traditionally, fluids were restricted to two-thirds of total daily maintenance in patients who had bacterial meningitis.
  - To minimize brain edema and prevent SIADH, which has been reported to occur in 29%–88% of cases of bacterial meningitis.

- Some studies have found that plasma antidiuretic hormone concentrations return to normal in patients with bacterial meningitis who receive replacement plus maintenance fluids for 24 hours.
  - — Concentrations remain high in patients restricted to two-thirds of maintenance requirements.

- Dehydration probably produces appropriate increase of antidiuretic hormone, but SIADH may still occur in non-dehydrated or fluid-replete children.
  - SIADH occurs in bacterial meningitis; however, no firm evidence has been found that fluid restriction prevents it.
- Maintenance fluids are believed necessary to perfuse, oxygenate, and deliver host defenses to the CNS.
- Obvious fluid deficits should be rapidly corrected.
- Serum sodium concentrations should be closely monitored several times during the first 24 hours of therapy, along with measurements of urine specific gravity.
  - If serum sodium concentration decreases to <125 mEq/L, the test should be repeated as soon as possible.
  - If the serum sodium concentration is still <125 mEq/L, fluids should be restricted to keep the vein open until serum electrolyte concentrations have been corrected.
  - Otherwise, for bacterial meningitis, providing routine maintenance fluids (eg, 0.45% saline with added potassium and dextrose) and ~80% of maintenance rate after fluid repletion and advancing to full maintenance rates as serum sodium increases to >135 mEq/L seems to be appropriate.
- The period of fluid restriction may only need to be ≤1 day.

Anti-inflammatory Therapy

- Use of glucocorticoids as adjunctive therapy in patients who have bacterial meningitis continues to be controversial.
  - Dexamethasone most likely improves hearing and neurologic outcomes of children with bacterial meningitis caused by Hib.
  - The usefulness of dexamethasone therapy in children and adults with bacterial meningitis caused by *S pneumoniae* or *N meningitidis* is less certain.
- Glucocorticoid therapy may also cause
  - Gastrointestinal bleeding
  - Decreased penetration of antimicrobial agents into the CSF
  - Obfuscation of the clinical assessment of children's response to therapy
- Dexamethasone may be beneficial when administered before or within 1 hour of the first dose of antimicrobial agents to infants and children ≥6 weeks with Hib meningitis.
- Dexamethasone should be considered for children who have pneumococcal meningitis, although uncertainty exists regarding benefits and risks.

Antimicrobial Therapy

- Empirical guides to therapy are primarily based on age because knowing which causative agent is present at the time of diagnosis of bacterial meningitis is difficult.
  - Adjustment to therapy can be made as conjugate vaccination history and results of CSF Gram stain and culture are confirmed.
- **Table 4** lists recommendations.

Antimicrobial Selection

- Dexamethasone can decrease CSF penetrance (and, thus, the activity) of vancomycin, and some experts, therefore, advise that
  - Dexamethasone should be omitted altogether *or*
  - Rifampin *plus* vancomycin *plus* a third-generation cephalosporin should be used with dexamethasone.
- Up to 40% of pneumococcal isolates may be resistant to penicillin at some level.
  - Many also are resistant to third-generation cephalosporins.
  - Therefore, infants and children suspected of having bacterial meningitis caused by pneumococci should receive vancomycin in addition to ceftriaxone or cefotaxime.
- As soon as the antimicrobial susceptibility of an isolate is known, vancomycin should be discontinued if the isolate is susceptible to penicillin or if it is nonsusceptible to penicillin but still susceptible to third-generation cephalosporins.
  - Vancomycin is continued with ceftriaxone or cefotaxime for isolates found to be nonsusceptible to penicillin and the third-generation cephalosporins.
    - — Rifampin is added to the combination in some circumstances.
    - — Consultation with an infectious diseases subspecialist is suggested.

Table 4. Antimicrobial Therapy of Bacterial Meningitis

Part A. Empirical Therapy Pending Culture and Susceptibility Data		
Age	**Likely Pathogens**	**Antimicrobial Agent**
0–1 mo	*Streptococcus agalactiae, Escherichia coli, Listeria monocytogenes*	Ampicillin + cefotaxime *or* ampicillin + aminoglycoside
1–3 mo	*S agalactiae, L monocytogenes, Streptococcus pneumoniae, Neisseria meningitidis, Haemophilus influenzae* type b	Ampicillin + (cefotaxime *or* ceftriaxone) *plus* vancomycin
3 mo–21 y	*S pneumoniae, N meningitidis* (*H influenzae* type b if not vaccinated)	(Ceftriaxone or cefotaxime) *plus* vancomycin

Part B. Specific Therapy	
Pathogen	**Therapy**
Streptococcus agalactiae	Ampicillin or penicillin G for 14–21 days; first 3 days, add gentamicin; cefotaxime also acceptable.
Listeria monocytogenes	Ampicillin for 14–21 days; first 3 days, add gentamicin.
Streptococcus pneumoniae	Penicillin MIC ≤0.06 mcg/mL and ceftriaxone or cefotaxime MIC ≤0.5 mcg/mL: penicillin G or ampicillin for 10–14 days; ceftriaxone or cefotaxime also acceptable
	Penicillin MIC ≥0.12 mcg/mL and ceftriaxone or cefotaxime MIC ≤0.5 mcg/mL: ceftriaxone or cefotaxime for 10–14 days
	Penicillin MIC ≥0.12 mcg/mL and ceftriaxone or cefotaxime MIC ≥1.0 mcg/mL: (ceftriaxone or cefotaxime) + vancomycin ± rifampin for 10–14 days
Neisseria meningitidis	Penicillin G for 7 days; alternatives: ampicillin, ceftriaxone, cefotaxime
Haemophilus influenzae type b	Ceftriaxone or cefotaxime for 10 days; alternative: ampicillin if isolate is susceptible

Part C. Antimicrobial Dosage			
	Dose (mg/kg/d)		
Agent	**Age 0–7 d**	**Age 8–28 d**	**Infants and Children**
Ampicillin	150–200 divided every 8 h	200–300 divided every 6 h	200–300 divided every 6 h
Cefotaxime	100 divided every 12 h	200 divided every 8 h	200–300 divided every 6 h
Ceftriaxone	Not recommended	80–100 divided every 12–24 h	80–100 divided every 12–24 h
Gentamicin	5 divided every 12 h	7.5 divided every 8 h	7.5 divided every 8 h

Table 4 (*continued*)

Part C. Antimicrobial Dosage (*continued*)			
Agent	Dose (mg/kg/d)		
	Age 0–7 d	Age 8–28 d	Infants and Children
Penicillin G	100,000–150,000 units divided every 12 h	150,000–200,000 units divided every 6 h	300,000–400,000 units divided every 4–6 h
Rifampin	10 divided every 12 h	20 divided every 12 h	20 divided every 12 h
Vancomycin	20 divided every 12 h	30 divided every 8 h	40–60 divided every 6 h

Abbreviation: MIC, minimum inhibitory concentration.

- In areas with low prevalence of penicillin-nonsusceptible pneumococci, providing a third-generation cephalosporin alone (without vancomycin) for empiric therapy is reasonable.
  - Especially when examination of the CSF Gram stain shows absence of gram-positive cocci.
  - Suspected or proven Hib disease may be treated reliably with ceftriaxone or cefotaxime.
  - Ampicillin may be used only if the isolate is known to be susceptible.
  - Disease caused by *N meningitidis* is treated with
    - Penicillin G at high doses *or*
    - Ampicillin *or*
    - A third-generation cephalosporin
- Meningitis caused by *N meningitidis* is usually treated for 7 days.
  - That caused by Hib is treated for 10 days.
  - That caused by *S pneumoniae* is treated for 10–14 days.
    - A 7-day course of antimicrobial therapy for uncomplicated Hib and *S pneumoniae* meningitis may also be effective.
  - Chloramphenicol is now rarely used in the industrialized world.
  - If an alternative agent beyond ampicillin or third-generation cephalosporins is required, meropenem may be administered.
    - Consultation with an infectious diseases specialist is suggested.

Assessment of Therapeutic Success

- Most failures are caused by
  - Inadequate therapy with the correct antimicrobial agent
  - Resistant organisms
  - Long delay in diagnosis
- Repeat lumbar puncture performed after therapy is completed does not reflect the adequacy of therapy or predict likelihood of recurrence.
  - Usually not indicated.
  - Delay in sterilizing the CSF beyond 24–36 hours has been associated with adverse outcomes; therefore, another lumbar puncture may be performed at that time.
  - Repeat lumbar puncture at 24–48 hours is indicated if drug-resistant *S pneumoniae* is present, especially if dexamethasone is administered.

Neonatal Meningitis

- Principles of antimicrobial therapy are the same as for infants and children.
  - Because organisms are different, antimicrobial selection must be adjusted.
- The ideal antimicrobial agent would be effective against
  - *Escherichia coli* and other enteric organisms
  - Group B β-hemolytic streptococci and other gram-positive organisms
- Cefotaxime and ceftriaxone are extremely active against organisms that usually cause neonatal meningitis, with the exception of *Listeria monocytogenes.*
  - Ceftriaxone has a much longer serum half-life than cefotaxime.
  - Ceftriaxone is highly protein bound and can displace unconjugated bilirubin from albumin and, thus, is generally not used in
    - Preterm neonates at risk for kernicterus
    - Term neonates with hyperbilirubinemia and who have no other suitable antimicrobial agent available with which to treat their infection

- No formal comparison has been made of these newer agents with the historical regimen of ampicillin plus an aminoglycoside, such as gentamicin.
- Cefotaxime plus ampicillin (to empirically treat *Listeria*) should be used to treat suspected neonatal meningitis.
  - Some authorities would add gentamicin as a third agent if gram-negative enteric meningitis were thought likely.
- Some enteric pathogens, such as *Pseudomonas aeruginosa* and Enterobacteriaceae, readily become resistant to third-generation cephalosporins.
  - These antibiotics should not be used empirically for all cases of suspected sepsis in neonates.
  - Choice of empiric ampicillin with gentamicin remains appropriate when the CSF appears typical.
- Intraventricular antimicrobial therapy.
  - Role remains uncertain and may even be harmful.
- Other therapeutic considerations are the same for neonates as for infants and children with bacterial meningitis.
  - No data support use of dexamethasone in neonates and infants <6 weeks.
- Head circumference should be measured serially to detect early signs of hydrocephalus.
- Conflicting data have been reported on whether IVIG is helpful.
  - At present, it does not have a defined role.

Aseptic Meningitis

- Mainly supportive.
- No specific anti-enteroviral agents are currently available.
- Meningoencephalitis caused by herpes simplex or varicella-zoster viruses should be treated with acyclovir.
- Aseptic meningitis caused by one of the other less common organisms may require specific therapy.

Tuberculous Meningitis

- Treatment of tuberculous meningitis depends, in part, on the rates of local drug resistance among *Mycobacterium tuberculosis* isolates; for drug-susceptible strains, treatment includes
  - 2 months of isoniazid, rifampin, pyrazinamide, and ethambutol (or ethionamide) once daily.
  - Followed by 7–10 months of isoniazid and rifampin, once daily or twice per week, for a total treatment duration of 9–12 months.
  - Although evidence for corticosteroid use in tuberculous meningitis in young children is lacking, in older adolescents, dexamethasone or prednisone adjunctive treatment for several weeks seems to decrease mortality, although not necessarily morbidity.

WHEN TO ADMIT

- All patients with suspected or proven meningitis should be hospitalized for evaluation and management.
- Patients with bacterial, fungal, or tuberculous meningitis should be transferred to a facility experienced in management of critically ill children, with availability of consultation by pediatric critical care, infectious diseases, neurologic, and neurosurgical subspecialists, which is especially important in neonatal meningitis.
  - Treatment must begin at the referral hospital.
- Infants and toddlers with viral meningitis may be hospitalized at a primary care–level hospital.
  - Transfer to a referral facility may be required for complicated cases (eg, uncertainty in diagnosis, slow resolution, presence of immune compromise).
- Older children and adolescents with viral meningitis do not always require hospitalization if
  - CSF evaluation strongly suggests bacterial disease is not present.
  - Adequate hydration and pain control can be undertaken at home.
  - Follow-up with the physician can be ensured.

WHEN TO REFER

- All patients with bacterial, fungal, or tuberculous meningitis should be treated in consultation with
  - Pediatric infectious disease subspecialists
  - Pediatric neurologic, critical care, and neurosurgical subspecialists, if required
- Patients with viral meningitis in whom unusual features or complications are present (eg, immune compromise, unexpected severity, slow resolution of illness, possibility of nonviral aseptic meningitis) should be referred to pediatric infectious diseases and neurology specialists.
- Patients with neonatal meningitis should be referred to pediatric infectious diseases, newborn medicine, and neurologic subspecialists.

COMPLICATIONS

- Early in the course of bacterial meningitis, the following complications may occur:
  - Increased intracranial pressure
  - Septic shock
  - Disseminated intravascular coagulation
  - Cardiorespiratory arrest
- Subdural effusions occasionally cause seizures or focal neurologic deficits.
  - In such cases, fluid should be removed by subdural taps.
  - Such effusions are rarely infected directly.
  - Subdural empyemas are occasionally reported.
- SIADH can complicate bacterial meningitis.
  - Patient should be monitored carefully for this complication.
  - If it occurs, fluid should be sharply restricted.
- Brain abscess is extremely rare after bacterial meningitis, except in neonates with meningitis caused by *Citrobacter* or certain *Enterobacter* species.
- Complications of neonatal meningitis are similar to those seen among older infants but are perhaps more common.
  - Hydrocephalus
  - Deafness
  - Blindness

PROGNOSIS

- Encephalitis mortality
  - Despite the appropriate use of bactericidal antibiotics, the mortality rate for bacterial meningitis remains 5%–10%.
  - Case-fatality rate for neonates generally ranges from 5%–25%.
  - In general, mortality is lower for full-term neonates than for low birth weight neonates (<2,500 g).
    - The case-fatality rate may approach 50% in low birth weight neonates with gram-negative enteric meningitis.
  - The case-fatality rate falls to ~5% for neonates who survive the first 24 hours.
  - Mortality of bacterial meningitis varies by pathogen.
    - 21% for *S pneumoniae*
    - 3% for *N meningitidis*
    - 6% for Hib
- ~15%–25% of survivors will have long-term morbidity, including
  - Developmental delay
  - Seizure disorder
  - Spasticity
  - Hearing loss
- ~65% of survivors of coliform meningitis are normal 3–7 years after illness.
  - ~15%–30% have mild to moderate neurologic sequelae.
  - 5%–10% have major sequelae.
- ~55% of group B β-hemolytic streptococcal meningitis survivors are normal.
  - 25% have mild to moderate sequelae.
  - 20% have major sequelae, such as
    - Hydrocephalus
    - Seizures
    - Profound intellectual disability
- As many as 80% of neonates who have gram-negative enteric meningitis caused by *Citrobacter* or certain *Cronobacter* (formerly *Enterobacter*) species will develop single or multiple brain abscesses.
  - Unusual in meningitis caused by any other organism.
  - Routine follow-up with cranial CT is indicated for neonates with meningitis or sepsis caused by *Citrobacter* species or *Enterobacter sakazakii.*
- All neonates recovering from meningitis should have careful audiologic testing and close evaluation for attainment of developmental milestones.
- Outcome of aseptic meningitis relates to the causative agent and child's age.
  - Patients with enteroviral meningitis usually recover completely.
  - However, some studies have reported low intelligence and delayed speech development after enteroviral meningitis in very young infants.
  - In light of these findings, prognosis for an infant <3 months is somewhat guarded.
  - The child's development should be monitored carefully.
  - In general, when encephalitis accompanies aseptic meningitis, the clinical course is more severe and the chance of sequelae increases.
- Predicting long-term sequelae for an individual child is difficult at the time of hospital discharge.
  - Some children who are apparently typical are later found to have hearing or learning deficits or develop a seizure disorder.
  - Conversely, some children expected to have a dismal prognosis based on abnormal neurologic examinations make remarkable gains.

- The practitioner should be guardedly optimistic with family while remaining sensitive to possible sequelae.

- Hearing should be tested formally before discharge from the hospital.
  - Most sensorineural hearing loss can be detected at this time.
  - The rate of persistent bilateral or unilateral sensorineural hearing loss is
    - 31% after pneumococcal meningitis
    - 10.5% after meningococcal meningitis
    - 6% after Hib meningitis
  - In young infants, auditory brain stem response or otoacoustic emissions testing is necessary for screening.
  - In older toddlers and children, conditioned response, play, or conventional audiometry may be performed.
  - Current thinking asserts that much of the hearing loss in meningitis occurs soon after infection.
    - This may explain why not all studies have shown reduction of hearing loss by dexamethasone therapy.
- Timing of other neurologic sequelae is less certain.

PREVENTION

- Some contacts of patients who have *N meningitidis* or Hib meningitis are at increased risk for the disease and should, therefore, receive prophylaxis.
- Whether all contacts of patients who have Hib meningitis should receive prophylaxis remains controversial.
- The American Academy of Pediatrics recommends that rifampin be provided to all household contacts, including adults, in households that have ≥1 contact <4 years whose immunization status against Hib is incomplete.
  - Definition of *complete immunization* depends on the age of the individual involved.
  - A household contact is
    - Anyone who resides with the index patient *or*
    - A nonresident who spent ≥4 hours a day with the index patient for 5 of the 7 days before the patient was hospitalized
- Prophylaxis for all household contacts, regardless of age, is provided in households with an infant <12 months.
  - Prophylaxis for non-household contacts of Hib disease does not appear to be necessary.
  - The index patient should receive rifampin during or at completion of treatment for Hib or meningococcal meningitis, unless ceftriaxone was used for treatment.
    - Many authorities still recommend that the index patient should receive rifampin during or at completion of treatment for Hib or meningococcal meningitis.
- The 1990s marked the beginning of the conjugate vaccine era.
  - With widespread use, these vaccines have dramatically decreased the incidence of invasive Hib disease.
  - Similarly, use of meningococcal polysaccharide-protein conjugate vaccine promises a marked decrease in invasive meningococcal infection.
- 1 of 3 Hib conjugate vaccines or 1 of 3 Hib conjugate-containing combination vaccine products is routinely provided to US infants beginning at 2 months of age.
- Pneumococcal conjugate vaccine is recommended for routine universal administration to infants and children <2 years.
  - Pneumococcal conjugate vaccine is also suggested for high-risk children 2–5 years of age, including children with
    - Sickle cell disease
    - Functional or anatomic asplenia
    - Immunosuppression
    - Cancer
    - Chronic renal disease
    - Chronic cardiopulmonary disease
    - CSF leaks
    - Diabetes
- At present, 1 of 2 tetravalent meningococcal polysaccharide conjugate vaccines is routinely used only for children and adults at high risk of disease, including
  - Young adolescents 11–12 years of age (with a booster dose in late adolescence)
  - Those with sickle cell disease, functional or anatomic asplenia, immunosuppression, or CSF leaks
- Meningococcal conjugate vaccines (tetravalent or bivalent) are also used for selected young infants and children at higher risk of disease and as an adjunct to chemoprophylaxis in outbreak control.
- Two new meningococcal serogroup B vaccines were licensed for use in the United States in early 2015.

Meningoencephalitis

DEFINITION

- Infection of the meninges and underlying brain parenchyma
- Can be classified as septic or aseptic
  - Septic
    - Meningitis caused by bacteria, fungi, and mycobacteria
    - Characterized by high fever, altered mental status, and purulent cerebrospinal fluid (CSF)
  - Aseptic
    - Aseptic meningitis and encephalitis.
    - Most often caused by viral infection; less frequently by parasites, spirochetes, rickettsia, and prions.
    - Encephalitis has also been implicated as a sequela of immunization or neoplasm; organisms located in the subarachnoid space may spread to the adjacent cortical mantle.
    - When there are signs of meningeal and cerebrocortical involvement, the term *meningoencephalitis* is appropriate.

SIGNS AND SYMPTOMS

General Features

- Depending on the extent of infection, the patient may have signs and symptoms of meningitis, encephalitis, or myelitis.
  - Children with aseptic meningitis, in contrast with meningoencephalitis, have intense headache, meningismus, and photophobia but may have clear sensorium.
  - Ameba, fungi, and viruses causing eastern equine encephalitis (EEE), herpes simplex virus (HSV), or rabies may result in
    - Cerebral or brain stem dysfunction
    - Intractable seizures
    - Increased intracranial pressure from brain edema
    - Death
- Most viruses spread via the bloodstream to the choroid plexus and from there to parenchyma of the cerebrum, brain stem, or spinal cord.
  - Rabies travels in a retrograde manner via peripheral nerves.
- Presenting signs and symptoms produced by viruses are often protean and include
  - Fever
  - Chills
  - Myalgia
  - Headache
- Clinical features of cerebral involvement include
  - Seizures
  - Altered mental status
- Encephalitis may produce focal neurologic findings.
  - If the spinal cord is involved, the patient may have
    - Symmetric limb paralysis.
    - Transverse sensory symptoms.
    - Bowel and bladder dysfunction.
    - Symptoms associated with a 2014 non-poliovirus enterovirus in Colorado in children included acute limb weakness and cranial nerve palsies.
- Viral infection of the central nervous system (CNS) may be occult.
  - CSF pleocytosis may or may not be present in meningoencephalitis.

Specific Viruses

- HSV commonly produces a necrotizing encephalitis.
  - Mothers of infected neonates often have no symptoms of herpes infection during or before gestation.
    - Makes diagnosis of neonatal infection more difficult
  - Classically infects the temporal lobes, resulting in olfactory seizures ("bad smells").
  - As the virus spreads from the temporal region, focal or generalized convulsive activity develops.
- Poliovirus selectively affects the motor neurons.
  - Paralysis of the respiratory muscles (bulbar paralysis) and extremities
    - Leg paralysis can be asymmetric but may be present in only 1% of infected patients.
    - ~5% of infected individuals have nonspecific sore throat, nausea, vomiting, and flu-like symptoms; 94% are asymptomatic.
- Varicella-zoster virus (VZV) and Epstein-Barr virus (EBV).
  - May infect cerebellum, producing an acute ataxia
- Congenital syphilis.
  - Rash develops on palms and soles in many instances.
- Arboviruses.
  - California virus encephalitis.
    - Suspect in a child living in a known endemic region with signs of fever and cerebrocortical dysfunction.
    - The course is usually mild.
  - Western equine encephalitis (WEE).
    - Primarily in infants
    - More severe syndrome than California virus

- EEE has a predilection for infants and young children.
- St Louis encephalitis occurs most often in epidemic form.
  - Produces illness in adults more often than in children
- The virus that causes Colorado tick fever produces dengue-like illness.
- West Nile virus
  - Children often develop signs of meningitis, whereas adults typically manifest signs of encephalitis.
- Lymphocytic choriomeningitis virus
  - May be asymptomatic in one-third of individuals or produce a clinical picture of aseptic meningitis, meningoencephalitis, or transverse myelitis.

- Rabies.
  - Long incubation period after a bite
    - Symptoms have been documented <30 days after transplantation of tissue from an infected individual.
  - Mental status changes
  - Seizures
  - Drooling
  - Choking on liquids (hydrophobia)
- Measles viruses.
  - Meningoencephalitis within 4–7 days after onset of rash
    - The severity of neurologic illness (including irritability, drowsiness, and ataxia) does not seem to be related to the intensity of systemic illness.
- Rubella.
  - Mild febrile exanthem of childhood with prominent arthralgia.
  - Infection during first trimester of pregnancy may result in congenital rubella syndrome.
  - A child affected with rubella in utero may be infectious for ≥12 months.
- Mumps meningoencephalitis.
  - Half of children are asymptomatic.
  - 15% may exhibit meningismus and headache.
  - May occur without parotitis, before the appearance of parotitis, or after it has resolved.
- HIV.
  - Infection may produce encephalitis or a progressive encephalopathy in children.
- Congenital syphilis.
  - Infected newborns may be asymptomatic or may present with
    - Hepatosplenomegaly
    - Petechial rash (blueberry muffin baby)
    - Rhinorrhea (snuffles)
    - Bony abnormalities
- Rocky Mountain spotted fever (RMSF).
  - Initial symptoms are protean, including fever and malaise.
  - Classic petechial rash develops by the fifth day.

DIFFERENTIAL DIAGNOSIS

- It is frequently challenging for the physician to distinguish "just a cold" from early stages of meningoencephalitis.
  - Change in mental status is the sine qua non of meningoencephalitis.
  - Toxins or metabolic derangement must be excluded.
    - Lead
    - Alcohol
    - Acetaminophen or other poisons
  - Differences in seasonal occurrence, clinical course, and outcome allow differentiation of some types of meningoencephalitis.
- Laboratory tests require time to establish diagnosis of meningoencephalitis.
  - Metabolic encephalopathy resulting from hypoglycemia, hyperammonemia, and Reye syndrome can be ruled out by appropriate laboratory investigations.
- Brain abscess.
  - The clinical course is usually slower.
  - Focal findings may be prominent.
  - History of sinus infection, middle ear or mastoid infection, or congenital heart disease may be elicited.
- Myelitic form of viral nervous system infection may be mimicked by mass lesion or Guillain-Barré syndrome.
- Congenital lymphocytic choriomeningitis may resemble congenital toxoplasmosis or cytomegalovirus (CMV) infection with chorioretinopathy, hydrocephaly, or microcephaly.
- Demyelinating diseases.
  - CNS demyelinating disease evolves over several days, producing
    - Altered mental status
    - Visual loss
    - Paralysis
    - Seizure

- Acute disseminated encephalomyelitis (ADEM)
  - — May present in children as a postinfectious inflammation of the brain and spinal cord.
  - — Varicella and rubella have been implicated as causes of ADEM, but in many cases, no definite virus is identified.
- Neuromyelitis optica (NMO)
  - — Prominent involvement of the optic nerve and spinal cord
- *N*-methyl-d-aspartate (NMDA) receptor antibody encephalitis
  - — May produce a syndrome similar to infectious encephalitis with altered sensorium, intractable seizures, movement disorder, and autonomic dysfunction

DIAGNOSTIC APPROACH

- Magnetic resonance imaging (MRI) with and without contrast is promptly performed in the child with suspected viral meningoencephalitis.
  - The spinal cord should also be imaged if signs of myelitis or radiculitis are present.
- Samples of CSF and blood are obtained for polymerase chain reaction (PCR), complete blood cell count and differential, glucose, and protein.
- Serologic tests should be obtained during the acute and convalescent phases of the disorder.
- Viral culture of CSF, throat, and stool should also be considered if PCR is not diagnostic.
- Every attempt should be made to identify the offending organism to
  - Help determine prognosis.
  - Document potential epidemic outbreaks.

LABORATORY FINDINGS

- CSF analysis.
  - However, there may be considerable overlap in the CSF formula that results from viral, bacterial, or fungal infection of the nervous system.
- Typical CSF alterations in patients with meningoencephalitis include
  - Mild to moderate pleocytosis
    - — May also be minimal or absent
  - Slight increase in protein level
    - — Varies with type of organism
  - No alteration in glucose concentration
    - — Degree of hypoglycorrhachia varies with type of organism.
- Erythrocytes in the CSF may indicate hemorrhagic brain necrosis.
  - Commonly seen with HSV infections and EEE
- Predominance of mononuclear cells in CSF is the exception in acute bacterial meningoencephalitis.
  - May be present with
    - — Syphilis
    - — Lyme disease
    - — Listeriosis
    - — Tuberculosis
    - — Facial nerve palsy caused by *Borrelia burgdorferi*
- HSV.
  - Elevation of both leukocytes (often granulocytes) and erythrocytes.
  - In a sample of 9 children with human herpesvirus (HHV) 6, CSF showed no increase in white blood cells and glucose and protein levels within reference ranges.
- Viral meningoencephalitis.
  - Leukocytes
    - — Initial predominance of polymorphonuclear neutrophils, followed by a shift to mononuclear cells
    - — Range, 0–2,000 cells/mm^3
  - Glucose
    - — >50% of serum concentration
  - Protein
    - — Mild to moderate increase
    - — Range, usually <200 mg/dL
  - Gram stain
    - — Negative
- Bacterial meningitis.
  - Leukocytes
    - — Predominantly neutrophils
    - — Range, 0–200,000 cells/mm^3
  - Protein
    - — Marked increase
    - — Range, usually >150 mg/dL
  - Gram stain
    - — Usually reveals bacteria
- PCR.
  - Powerful tool in identifying enterovirus, mumps virus, CMV, VZV, and other viruses.
    - — Positive PCR result may raise the question of whether the presence of viral antigen represents new or prior infection.
    - — Comparison of serum and CSF titer may be helpful in this situation.

- PCR of CSF in adults with herpes simplex encephalitis has >90% specificity and sensitivity.
  - The reliability of PCR in neonatal HSV may vary according to the assay used in a specific laboratory.
- Rapid-screening test for EBV (mononucleosis spot test) is available at most hospitals.
- Test results for HSV may be negative initially and positive in later analyses.
- In a small sample, HHV-6 was disclosed by PCR in ~25% of samples.

■ Viral culture of CSF.
- Advantage of detection of viruses not included in the PCR panel
- Disadvantage of having false negative results

■ Serum antibodies differentiate demyelinating disorders.
- Autoantibodies against myelin oligodendrocyte glycoprotein
  - May be present in 44% of patients with ADEM but only 2% with multiple sclerosis
- Serum aquaporin-4 antibodies
  - Differentiate NMO
- NMDA receptor antibodies
  - Anti-NMDA receptor antibody encephalitis.
  - One-third of teenaged girls with NMDA receptor encephalitis may have ovarian teratomas.

IMAGING

■ Prompt brain imaging in children suspected of having viral encephalitis is essential.
- Computed tomography, although rapid and widely available, lacks the sensitivity of MRI in discerning edema formation and inflammation.
- Even MRI may be normal in the early phases of meningoencephalitis.
  - Contrast should be administered to better assess inflammation or cerebral cortical enhancement.
  - The spinal cord should be imaged if signs of myelitis or radiculitis are present.

■ MRI.
- Viral encephalitis shows
  - Diffuse scattered or confluent areas of T2-weighted hyperintensities or T1-weighted hypointensities.
  - When encephalitis produces cerebral edema, MRI may disclose midline shift, ventricular compression, or cerebral cortical effacement.
- 2014 infectious encephalomyelitis outbreak in Colorado revealed
  - Nonenhancing lesions in the gray matter of the spinal cord or brain stem
- HSV infection
  - Temporal lobe enhancement or necrosis
- Rabies encephalitis
  - Cerebral edema
- ADEM
  - Marked signal abnormalities in the subcortical white matter, corpus callosum, cerebellum, brain stem, or spinal cord
- NMDA receptor encephalitis
  - Abnormalities in the white matter or brain stem

DIAGNOSTIC PROCEDURES

■ Electroencephalography
- Infants with HSV often have periodic (2-Hz) lateralized epileptiform discharges in the temporal region.

■ Brain biopsy
- Seldom used as a diagnostic tool

TREATMENT APPROACH

■ Viral meningoencephalitis
- After imaging and laboratory studies, intravenous (IV) acyclovir is considered in treatment of HSV, VZV, HHV-6, and CMV.
  - Renal function must be monitored because acyclovir is nephrotoxic.
- Corticosteroids are not of proven benefit in viral meningoencephalitis and may blunt host defenses.

■ Encephalitis caused by agents other than viruses is treated appropriately, as noted later in the chapter.

■ Supportive treatment includes
- Management of intracranial pressure
- Respiratory support
- Treating seizures
- Physical therapy
- Maintaining fluid and electrolyte balance

SPECIFIC TREATMENTS

■ HSV infection
- Acyclovir.
- Higher doses (60 mg/kg/d) recommended for neonates.
- Nephrotoxic; renal function must be monitored.

■ VZV infection
- Acyclovir
- Ganciclovir

- HHV-6
  - Acyclovir
  - Ganciclovir
- CMV
  - Acyclovir
  - Ganciclovir
- Rickettsial infection of the nervous system
  - Doxycycline
- *Borrelia* infection
  - Ceftriaxone
- Treponemal infection
  - Penicillin

WHEN TO ADMIT

- Patients with meningoencephalitis who have increased intracranial pressure, intractable seizures, and altered mental status

WHEN TO REFER

- Patients with meningoencephalitis who have increased intracranial pressure, intractable seizures, and altered mental status must be managed with the help of infectious disease and critical care medicine specialists.

FOLLOW-UP

- Renal function must be monitored during administration of acyclovir.
- Every child who has a documented or suspected viral nervous system infection must be carefully monitored for cerebral cortical dysfunction.
  - Auditory aftereffects
  - Visual aftereffects
  - Cognitive aftereffects

COMPLICATIONS

- The nonfatal meningoencephalitides of infancy (ie, those caused by enteroviral infection)
  - May result in substantial reductions in head circumference, intelligence, and learning ability
- California encephalitis
  - Causes emotional or learning disorders in 15% of affected children
- EBV
  - Focal epilepsy may be a sequelae of a mild encephalitis caused by EBV.
- Measles
  - An unusual syndrome of dementia and myoclonic seizures can develop in children 7–10 years after measles infection or immunization.
    - 4–11 cases per 100,000 cases of measles.
    - Results from persistent measles infection known as *subacute sclerosing panencephalitis.*
    - Infants and younger children are at higher risk than children >5 years.
    - Syndrome of subacute measles encephalitis has also been reported in immunosuppressed individuals.
- VZV
  - Reactivation may produce a number of neurologic syndromes, including encephalitis, myelitis, stroke, and acute infectious demyelinating polyneuropathy (Guillain-Barré syndrome).
- Congenital syphilis
  - Mother-to-child transmission may result in preterm birth or stillbirth.

PROGNOSIS

- The course and outcome of meningoencephalitis are related to the virulence of the organism and the host response to the infection.
  - Age
  - Neurologic status at time of treatment
  - Immune status
- Neurologic consequences may be lasting.
  - Enterovirus 71 infection of the CNS in children was associated with a nearly 7-fold increase in attention-deficit/hyperactivity disorder–related symptoms.
    - 20% of children with meningoencephalitis versus 3% of matched control subjects
- Respiratory syncytial virus encephalitis.
  - All children have a full recovery.
- Rabies.
  - Has highest case fatality of any infection.
  - Invariably produces meningoencephalitis.
  - Most reported cases of rabies encephalitis have been fatal.
- HSV necrotizing encephalitis.
  - Development of antiviral therapy has profoundly affected prognosis.
    - 50%–67% of untreated cases are fatal.
    - <5% of untreated patients who survive regain typical neurologic function.
    - No deaths were reported from childhood HSV encephalitis with acyclovir therapy.
  - Two-thirds of patients who survive with antiviral therapy have neurologic sequelae.
    - Epilepsy (44%)
    - Cognitive deficits (25%)
  - Infants with HSV-1 encephalitis have better neurologic outcomes than those infected with HSV-2.

- Developmental scores were significantly higher in infants with neonatal HSV who received oral suppressive therapy with acyclovir for 6 months after their initial IV course of antiviral therapy.

- EBV encephalitis.
  - Good neurologic outcome in 80%
  - Mild neurologic sequelae in 10%
  - Death in 10%
- EEE.
  - Most severe of the arboviral diseases.
    - Children are affected more severely than adults.
  - Frequently fatal (death in one-third of patients).
  - Many survivors suffer severe neurologic consequences.
- WEE.
  - Associated with complete recovery in adults
  - Causes death in 3% of children
  - Neurologic sequelae in ≥30% of children
- Japanese encephalitis.
  - Deaths may be 3-fold greater in children than adults.
- RMSF.
  - Children 5–9 years are at greatest risk of death, as are adults >70 years.
- Measles meningoencephalitis.
  - Mortality ~10%.
  - As many as half of survivors may have neurologic sequelae.
- Mumps meningoencephalitis.
  - Mild illness that generally has a good prognosis
- St Louis encephalitis.
  - Most infections are mild.

PREVENTION

- Prevention is the most cost-effective method of reducing morbidity and mortality caused by viral meningoencephalitis.
- Immunization
  - Has reduced, but not eliminated, poliomyelitis.
  - Has made rubella, mumps, and measles meningoencephalitis uncommon.
  - Repeat measles immunizations of older children should reduce the incidence of measles encephalitis and subacute sclerosing panencephalitis further.
- Prohibition of beef products in cattle feed has reduced incidence of new-variant Creutzfeldt-Jakob disease and bovine spongiform encephalopathy.
- Mosquito and other insect controls.

Metabolic Disorders Beyond the Newborn Period

DEFINITION

- Inborn errors of metabolism (IEMs) are conditions in which a change in a gene alters the function of an enzyme or other protein.
- The change in function causes alterations in a metabolic pathway that leads to clinical consequences.
- A block in a pathway can lead to
  - Increase of a compound normally present but toxic in excess (eg, ammonia or methylmalonic acid)
  - Inadequate levels of some essential metabolic product (eg, glucose, adenosine triphosphate for energy)
  - Production through an alternative pathway of a toxic compound that is not normally present

SIGNS AND SYMPTOMS

- IEMs can cause virtually any symptom or sign and can present at any age.
- May be static or may cause intermittent or progressive signs and symptoms.
- May present commonly with intellectual disability, failure to thrive, and symptoms of septicemia.
- The primary care physician routinely evaluates for IEMs in every healthy baby through newborn screening.
  - A normal newborn screen does not conclusively exclude an IEM.
  - Physicians should maintain a high index of suspicion for an IEM.
- Symptoms that raise suspicion include
  - Altered consciousness, especially recurrent episodes of abnormal mental status out of proportion to physical health
    - Lethargy without hypoxia, shock, or meningitis
    - Altered behavior, such as episodic irritability or inattention
  - Seizures in the first day of life or intractable seizures
  - Ataxia, especially recurrent, and any other movement disorder, especially dystonia
  - Exercise intolerance with pain or fatigue that interferes with reasonable activity
  - Regression in neurologic function, development, or behavior, including regressive autism spectrum disorder (ASD)
  - Unusual diet preferences or avoidances (eg, avoidance of protein or certain sugars), especially when intermittent or progressive symptoms and signs follow a diet change (eg, from human milk to formula)
  - Odors (maple syrup, sweaty feet, cat urine, mousy, rotten fish—each suggests a specific disorder)
  - Recurrent or persistent pain, including headaches, abdominal pain, and extremity pain
  - Sun aversion or sensitivity; heat intolerance
  - Family history of consanguinity or of a relative with symptoms or signs seen in IEM
    - Because most conditions are autosomal recessive, waiting for positive family history guarantees you will miss an opportunity to diagnose the index case in most families.
- Physical signs that raise suspicion include
  - Unusual tone: hypertonia in the neonate, hypotonia >1 year (and certainly >2 years), and mixed tone
  - Movement disorders (Watch carefully over a few minutes to see if the baby can be still for more than seconds.)
  - Areflexia
  - Decreased muscle mass or muscle quality
  - Organomegaly
  - Microcephaly or macrocephaly
  - Odors
  - Cataracts and retinopathy
  - Coarse features
  - Widening of joints, kyphosis, joint contractures
  - Coarse or otherwise unusual hair, unusually thick skin, unusual rashes, including sun sensitivity
- History/physical examination.
  - Ask about tolerance of exercise and typically mild childhood illnesses.
  - Ask whether there is any association of symptoms with changes in diet or whether there are unusual cravings or aversions.
  - Note any "red flag" symptoms.
  - An IEM is more likely when there are problems in >1 organ or system, even if there seems to be a simple explanation for each problem.
  - Measure head circumference, even in the older child or adolescent.
  - Examine for unusual texture of hair or unusual rashes.

- Pay careful attention to movement and eyes.
  - Assess eyes for cloudiness or haziness.
  - Consider an ophthalmologic evaluation to assess for other signs (eg, retinopathy in the lens, cornea, or retina).

DIFFERENTIAL DIAGNOSIS

- Finding evidence of one condition, such as infection, does not exclude the presence of an IEM.
  - A child with a fatty acid oxidation disorder may present with acute metabolic crisis as a result of otitis or respiratory syncytial virus.
    - Neither should be assumed to explain altered mental status and abnormal liver function.
- IEMs can be confused with antecedent infection or hypoxia, whether or not there is good evidence for perinatal infection or neonatal asphyxia.
- Poisoning.
  - If poisoning is suspected, consider an IEM unless there is absolute evidence.
  - When there is convincing evidence for ingestion (eg, empty bottle of medications, symptoms that perfectly match a specific toxin), do not consider an IEM.
  - IEMs are basically a "self-poisoning" and should be considered when poison is in the differential diagnosis.
- Child maltreatment.
  - An IEM can mimic and coexist with maltreatment.
  - Menkes disease and glutaric aciduria type 1 present with subdural hematoma or retinal hemorrhages.
  - Many IEMs present with poor feeding and failure to thrive.
  - Some IEMs make maltreatment more likely because of irritability and other symptoms that can make care more challenging.
- Infection.
  - An IEM can present acutely as a result of an infection.
  - Consider whether observed or diagnosed infection sufficiently explains all symptoms and signs.
  - Recognize that most infections not involving the central nervous system do not cause altered neurologic status.
  - Some irritability is typical with fever, but extreme irritability or lethargy that does not improve with resolution should be a clue to an IEM.
- Acidosis should not be expected in a vomiting child unless there is severe diarrhea or poor perfusion.
- The first step is to include IEMs in the differential diagnosis of the child with diverse presentations (**Table 1**).

DIAGNOSTIC APPROACH

- The diagnostic approach to a child with a suspected IEM is specific to each presentation and to each condition.
- Although typically a collaborative effort, the nongenetic physician can begin the process using the history—including family history—and physical examination, followed by judicious use of laboratory studies.

LABORATORY FINDINGS

General

- Basic laboratory testing for an IEM involves little added cost for the patient who has acute or chronic neurodevelopmental or health problems.
  - Initial, include
    - Complete blood cell count (CBC)
    - Electrolytes
    - Liver enzymes
    - Urinalysis
  - Followed by these, when appropriate:
    - Blood amino acid levels
    - Urine organic acid (UOA) studies
    - Acylcarnitine profile (ACP)
    - Carnitine total and free levels
    - Properly collected ammonia and lactate levels
  - More specific laboratory testing can be useful.
- Laboratory testing for an IEM begins with a proper interpretation of test results.
  - Searching for evidence of an infection and investigating the level of illness by CBC, electrolytes, and urinalyses.
  - Recognition of the inappropriateness of an increased anion gap in a vomiting child.
  - Attention to mean corpuscular volume (MCV) may provide a clue to an IEM as a cause of metabolic acidosis, anemia, or failure to thrive.
  - Simple studies (eg, creatine phosphokinase, bilirubin fractionation).
- Ketones.
  - Consider whether urine ketones are appropriate for the child's medical status.
  - In the child who has not fasted and with failure to thrive, positive ketones are a clue to an IEM that produces elevated levels of an organic acid that cross-reacts with the reagent used to measure ketones.

(continued on page 709)

Table 1. Categories of Inborn Errors of Metabolism With Key Characteristics and Examples

Category	Definition, Biochemistry, and Genetics	Key Characteristics and Examples
Amino-acidopathies	Involve abnormal levels of amino acids with the amino group still attached; include primary catalytic defects, cofactor defects, transport defects (MSUD may be categorized here because amino acid levels are elevated in blood). Almost all are autosomal recessive.	Usually not acidotic (except MSUD, or with renal tubular acidosis of tyrosinemia). Typically, but not always, affect the CNS (eg, PKU, glycine encephalopathy); may affect other organs (eg, liver and renal tubules in tyrosinemia type 1). Episodic, static, or progressive. Homocystinuria may present with stroke or clotting, with or without intellectual disability. Diagnosis with blood AA (PAA or SAA), sometimes UAA, sometimes confirmed by enzyme assay or DNA testing. *Special presentation:* Mother with PKU or hyperphenylalaninemia may be normal and unaware of diagnosis but have babies with microcephaly and intellectual disability; this has nearly 100% recurrence risk, and adverse outcome is preventable with treatment of mother; diagnosed by blood AA in mother.
Organic acidemias	Involve metabolites of amino acids after amino group removed and other compounds with C, H, and O (fatty acids and lactate/energy in separate categories). Essentially all are autosomal recessive.	Usually, but not always, acidotic, anorexia/vomiting; episodic altered consciousness; may include bone marrow depression or other end-organ failure. Diagnosis with urine organic acids; blood ACP may be helpful; enzyme assays or DNA testing for confirmation when available.
Urea cycle defects	Involve the urea cycle, typically with altered levels of the amino acids in the urea cycle. Most are autosomal recessive, but the most common is X-linked.	Altered mental status, decreased appetite or intractable or recurrent emesis including "cyclic vomiting," migraine, ataxia, and often with protein aversion. Typically not acidotic unless in shock; respiratory alkalosis is common. Diagnosis by blood AA, in some cases confirmed with enzyme assays or DNA testing.
Fatty acid oxidation and carnitine metabolism disorders	Involve the oxidation of fatty acids to ketones and the transport of fatty acids into the mitochondria for oxidation. Essentially all are autosomal recessive.	Classic presentation is Reye syndrome or SIDS in an infant or toddler, but more commonly the presentation is excessive irritability or lethargy with ordinary childhood illness or extended fasting. The hallmark is hypoketosis, but some ketones are usually present, and hypoglycemia is only sometimes present. Also may present (especially long-chain fatty acid oxidation and carnitine metabolism) with liver failure, failure to thrive, cardiomyopathy, or rhabdomyolysis; retinopathy and bone marrow failure may occur. Diagnose with ACP, but that may be normal when well, and diagnose some conditions with carnitine levels. Some diagnoses may be confirmed with enzyme assays or DNA testing.

Table 1 (*continued*)

Category	Definition, Biochemistry, and Genetics	Key Characteristics and Examples
Mitochondrial (energy) metabolism and disorders of lactate and pyruvate	Include oxidative phosphorylation defects of the mitochondrial respiratory chain, defects of the Krebs cycle and of PDH and pyruvate carboxylase. May occur because of defects of single enzymes, of transport into the mitochondria (of enzymes or substrate), of cofactor synthesis (eg, coenzyme Q), of multiple enzymes because of mutations in mtDNA, or of mtDNA repair or synthesis. X-linked inheritance (PDH deficiency and some creatine disorders), autosomal-dominant inheritance, and maternal inheritance because of mtDNA mutations occur, but most conditions are autosomal recessive.	Any presentation, any age, with variability in biochemical findings and clinical presentation. Examples include dysmorphic features with brain dysgenesis or porencephalic cysts; the normally formed neonate with overwhelming acidosis; Leigh disease (an infantile or childhood-onset brain stem neurodegenerative disease); isolated organ failure of heart, liver, kidney, exocrine pancreas, bone marrow, retina, or others; and combinations (eg, Pearson syndrome [bone marrow and exocrine pancreatic failure], multisystem failure). Other classic pediatric conditions are MELAS, MERRF, and Alpers disease (progressive seizures and liver failure). Diagnostic testing depends on presentation; usually begins with blood AA and UOA, lactate and pyruvate, and ACP; but, in some cases, the first diagnostic test is in DNA in blood or biopsy of muscle or liver for histochemistry or enzyme assays. It is well described that enzyme assays or DNA can be normal in cases with proven disease.
Carbohydrate disorders	Involve metabolism of sugars (with glycogen storage disorders separated out); examples are galactosemia and the disorders of fructose metabolism. Essentially all are autosomal recessive.	Typically presenting with liver disease or hypoglycemia and acidosis, often with renal tubular disease. Cataracts may be seen in galactosemia at presentation in some cases and develop in untreated cases. Diagnosis based on enzyme assay or DNA testing.
Glycogen storage disorders	The various disorders of glycogen synthesis and degradation; when glycogen is not normally branched, there are adverse effects on the liver. Most are autosomal recessive, and some are X-linked.	Typically, but not always, including hepatomegaly, 2 major presentations are seen, with hypoglycemia (eg, GSD type 1) or with muscle weakness with or without cardiomyopathy and rhabdomyolysis (Pompe disease, McArdle disease). Some conditions lead to liver failure or liver tumors. However, glycogen synthase deficiency is GSD type 0 and presents as ketotic hypoglycemia with a small liver. Diagnosis by histology, enzyme assay, and DNA testing for some conditions.
Porphyrias	Disorders of metabolism of the porphyrins in synthesis or degradation of hemoglobins. AIP is autosomal dominant; others are recessive or X-linked.	Most cases present in late childhood or adolescence, with or without skin findings, but some types present in the neonate. CNS is typically spared, but AIP and hepatic coproporphyria can present with psychotic episodes, recurrent abdominal pain, and peripheral neuropathy, often diagnosed as psychosomatic disease. Diagnosis includes biochemistry, enzyme assay, and DNA testing for some conditions.

Table 1 (*continued*)

Category	Definition, Biochemistry, and Genetics	Key Characteristics and Examples
Lysosomal storage diseases	Disorders resulting from alteration of function of individual enzymes responsible for breaking down large cell wall molecules (mucopolysaccharides, glycolipids, sphingolipids) within the lysosome, or of import into the lysosome affecting multiple pathways. Most are autosomal recessive, and Hunter syndrome and Fabry disease are X-linked.	Progressive disorders that until recently were untreatable. Some affect the CNS only (Krabbe disease), whereas others also have organomegaly (Tay-Sachs disease), dysmorphic features, and skeletal changes (the mucopolysaccharidoses, except for Sanfilippo syndrome that affects primarily CNS). Cystinosis affects bone by causing renal tubular disease. Hepatosplenomegaly of Gaucher disease leads to preventable anemia and thrombocytopenia. Fabry disease is especially underdiagnosed and untreated; it causes renal failure (typically in early or middle adulthood), cardiomyopathy, stroke, and pain from peripheral neuropathy; enzyme infusion prevents permanent damage. Diagnose by biochemistry (eg, UMPS or oligosaccharides in some), enzyme assay, DNA testing for some conditions, or carrier testing, which is available for some conditions.
Peroxisomal disorders	Disorders of individual enzymes in the peroxisome involved in various pathways, including very long-chain fatty acid oxidation and plasmalogen synthesis, or defects of peroxisome development leading to multiple pathway dysfunction	A wide variety of presentations, including the neurodegenerative condition adrenoleukodystrophy or isolated primary adrenal failure. May present as a dysmorphic syndrome; as Zellweger syndrome; with Down syndrome–like facies, hypotonia, and liver and renal cysts; and as progressive neurodegenerative disease. Most have alteration of either very long-chain fatty acids, plasmalogens, or pipecolic acid, and some have stippled epiphyses on plain film. Diagnose with histology and biochemistry and with DNA testing in some conditions.
Disorders of purines and pyrimidines	Disorders of synthesis or degradation; include disorders of uric acid metabolism. Autosomal recessive or X-linked.	Variable presentation, mostly affecting the CNS or bone marrow (eg, severe combined immunodeficiency). Include Lesch-Nyhan syndrome, with self-mutilation; the same enzyme defect in milder cases causes gout. Diagnose with biochemistry; DNA testing in some conditions.
Neurotransmitter disorders (and other conditions evident only on analysis of cerebrospinal fluid)	Conditions in which critical neuroactive molecules are not properly synthesized or metabolized. Include a number of conditions in which cofactor metabolism is the primary problem, including vitamin B_6 responsive seizures and disorders of pterin metabolism. Most are autosomal recessive.	By definition, these conditions affect function of the central or peripheral nervous system. Typical presentations include seizures, irritability or other altered mental status, and abnormalities of tone and development. Indirect evidence may be present (eg, low prolactin in blood resulting from low dopamine or response to pyridoxine trial), but, in general, spinal fluid collected and handled with special precautions is needed for diagnosis. Diagnosis by biochemistry of spinal fluid; some can be confirmed with enzyme assay or DNA testing.

Table 1 (*continued*)

Category	Definition, Biochemistry, and Genetics	Key Characteristics and Examples
Disorders of metals and micronutrients	Conditions that involve altered metabolism of metals, and some micronutrients, including iron, copper, and molybdenum; they can involve excess storage or inability to incorporate metal into enzymes for which it is a critical component. Recessive or X-linked and in some forms of hemochromatosis complex with asymptomatic homozygotes and symptomatic heterozygotes.	Disorders of copper include Menkes disease (neonatal seizures with unusual hair) and Wilson disease (progressive CNS or liver disease). Disorders of iron in pediatrics include neonatal hemochromatosis, presenting with liver disease, or rare late childhood presentation of classic hemochromatosis, causing initial nonspecific symptoms resulting in arthritis or single or multiple organ failure (typically liver, heart, or diabetes). This list does not attempt to consider the primary disorders of molybdenum, zinc, and other micronutrients. Diagnose with metal levels, other biochemistry, histology, and histochemistry; DNA testing in some conditions.
Disorders of connective tissue (collagen, fibrillin, elastin)	Not to be mistaken for the term *connective tissue disorder,* meaning autoimmune disorders, these are typically disorders of structural proteins that affect the integrity of the connective tissue of selected or all organs. Recessive, dominant, or X-linked.	Usually considered in general genetics. Abnormal collagen may primarily affect bones causing osteogenesis imperfecta (with or without dental and hearing problems) or may affect joints and skin, with some causing rupture of vessels or hollow organs. Fibrillin mutations cause Marfan syndrome, and elastin mutations cause Williams syndrome. Diagnosis is by clinical evaluation; in some cases confirmed by DNA testing or by biochemistry of the altered molecule in tissue.
Carbohydrate-deficient glycoprotein disorders	Disorders that involve multiple biochemical pathways because the primary disorder is a failure of one or more enzymes that attach carbohydrate moieties to proteins (including enzymes) required for correct structure and function of the protein. Most are autosomal recessive.	As a group, there are now >30 conditions identified with highly varied presentation, including conditions with dysmorphic features and malformations evident in the neonate, and others that present only much later; the classic "type 1A" has cerebellar hypoplasia. Often with involvement of the CNS and peripheral nervous system, and includes some primary muscular dystrophies. Some have acute episodes of metabolic crisis or organ failure, and many have FTT. Diagnosis is by examination in blood for altered pattern of carbohydrates attached to various proteins; many can be confirmed by DNA testing and some by enzyme assay.
Channelopathies	Altered transport of ions across cell walls, especially including calcium. The classic disorder of transport, cystic fibrosis, is not typically considered an IEM but does fit the category. Recessive, dominant, or X-linked.	Leaving aside cystic fibrosis, the 2 major presentations of conditions in this category are neurologic (progressive ataxias, seizures, including heritable febrile seizures or progressive seizure disorders) or cardiac arrhythmias (including classic long QT syndrome). Typically without acidosis or altered organ function, except for the primary presentation. Diagnosis is clinical, confirmed in some cases by DNA testing.

Table 1 (*continued*)

Category	Definition, Biochemistry, and Genetics	Key Characteristics and Examples
Disorders of cholesterol and other sterol metabolism (primarily synthesis)	Alteration in the synthesis of cholesterol and other sterols; pathophysiology may be because of inadequate amounts of an essential metabolite or interference from the abnormal metabolites. Typically autosomal recessive.	Presenting with FTT, neurologic disease, and, often, with birth defects and skin disease, this category includes a previously well-described autosomal-recessive dysmorphic syndrome (Smith-Lemli-Opitz syndrome). These disorders typically include feeding disturbance and hypotonia and may have skin pigment abnormalities. Diagnosis by biochemistry; cholesterol may be low, but measurement of cholesterol alone is not adequate to make or exclude a diagnosis of any of these conditions. Diagnosis depends on demonstration of abnormal patterns of sterols; some may be confirmed with DNA testing.
Disorders of vitamins and cofactors	Vitamins and other cofactors must be absorbed and transported across membranes, and many must be metabolized to an active form or synthesized in the human cell. Pathophysiology of these conditions depends on the pathway. Typically autosomal recessive, but X-linked and dominant disease is known.	This category crosses almost all boundaries because cofactors are found in many pathways. Presentation can be systemic or more limited to the nervous system, bone marrow, bones, muscle (including cardiac), or skin. As an example, problems with vitamin B_{12} (cobalamin) can alter amino acid metabolism, organic acid metabolism, or both. An abnormality of vitamin D leads to X-linked rickets, and an abnormality of pterin metabolism leads to autosomal-dominant dopa-responsive dystonia, also known to neurologists as Segawa syndrome. Failure to synthesize coenzyme Q10 leads to a particularly reversible disorder of energy metabolism. Diagnosis of a disorder of vitamin or cofactor metabolism is based on measurement of appropriate metabolites and on measurement of levels of specific vitamins or cofactors. In some cases, there is functional testing (eg, enzyme assay for biotinidase, enzyme assay and complementation studies for cobalamin disorders). Often can be confirmed by DNA testing.

Abbreviations: AA, amino acid; ACP, acylcarnitine profile; AIP, acute intermittent porphyria; CNS, central nervous system; FTT, failure to thrive; GSD, glycogen storage disease; IEM, inborn error of metabolism; MELAS, mitochondrial encephalopathy, lactic acidosis, and stroke; MERRF, myoclonic epilepsy, ragged red fibers; MSUD, maple syrup urine disease; mtDNA, mitochondrial DNA; PAA, plasma amino acid; PDH, pyruvate dehydrogenase; PKU, phenylketonuria; SAA, serum amino acid; SIDS, sudden infant death syndrome; UAA, urine amino acid; UMPS, urine mucopolysaccharide; UOA, urine organic acid.

- Absence or low levels of ketones in the urine of the catabolic child are a clue to an IEM that reduces ketone production.
- Thus, "typical urinalysis" in a child with history of significantly decreased intake suggests disorder of fatty acid metabolism.

- When an IEM is suspected, be aware that some test results depend on the status of the patient.
  - Biochemical samples collected while the patient is acutely symptomatic may be diagnostic.
  - Samples collected between episodes may be normal in some conditions and some patients.
  - This is especially true for some disorders of
    - Organic acids
    - Amino acids
    - Urea cycle
    - Mitochondrial conditions
    - Fatty acid oxidation
    - Some porphyrias
- Diagnostic samples should be collected promptly on presentation of a symptomatic child.
- Artifacts of sample collection are problematic for some tests, particularly lactate and ammonia.
- Some IEMs require analysis of cerebrospinal fluid (CSF) or of tissue, such as muscle, to measure analytes or for enzyme assay.
- Timing.
  - Consider IEM early in evaluation so that an appropriate sample can be collected if invasive testing is planned or performed.
- DNA studies can assist in the diagnosis of an IEM.
  - Can confirm specific diagnoses and replace invasive studies.
  - Discuss the interpretation (including sensitivity) with genetic experts if experience in interpreting these test results is lacking.
  - Consider whether the purpose of testing is to guide patient management or to determine whether to provide carrier testing to other family members.
  - It is most efficient to focus DNA testing on a specific condition or panel of disorders.
  - DNA testing varies in sensitivity, depending on the condition and the method used in testing.
    - The likelihood that DNA testing will identify a condition that is present may be >95%.
    - For other conditions sensitivity is substantially lower, and in some the specific gene is not identified or testing is not available.
    - Abnormal DNA results can confirm a diagnosis, especially for X-linked and autosomal-dominant conditions.
  - For autosomal-recessive conditions, the finding of 2 different disease-causing mutations is diagnostic if there is evidence that the 2 mutations are not on the same chromosome.
  - Normal results of DNA testing seldom completely exclude a diagnosis but can be used to adjust the differential diagnosis.
  - DNA testing of family members is not always necessary and can lead to problems.
    - Some laboratories and some jurisdictions require patient/parental consent for DNA testing.
    - Paternity.
      - It may be possible to find nonpaternity with DNA testing.
      - If only the patient is tested, nonpaternity could be identified only if a parent was previously tested.
  - Mitochondrial DNA.
    - Certain mutations provide information about risk for the mother and maternal relatives, even if they are symptom free.
    - Specific counseling should be done before testing is performed, whether or not required by the state or the laboratory.
  - Cost.
    - Sample handling for DNA testing is not particularly difficult, so collection may be simple.
    - Testing should not be done without considering coverage so that family and physician are not exposed to unexpected costs.
  - If the physician is not comfortable providing complete pretest counseling, the assistance of a genetics professional should be sought.

Test Results That Raise Suspicion of IEM

- Electrolytes and renal function (note anion gap).
  - Acidosis out of proportion to clinical status, especially, but not exclusively, high anion gap acidosis (Renal tubular acidosis can be the result of an IEM.)
  - Alkalosis (Suspect hyperammonemia.)
  - Low blood urea nitrogen (may indicate inability to make urea via the urea cycle)
- Glucose that is low in a previously healthy child with normal growth.
- Hyperammonemia in a child with altered mental status (if ammonia is measured); caution in sample collection.

- Urinalysis for inappropriate pH or ketosis.
  - Ketones positive in the neonate or non-fasting older child can indicate an IEM because the method of testing for "ketones" in urine does not distinguish between β-hydroxybutyrate and other organic acids, such as methylmalonic or propionic acids.
  - Ketones negative or only minimally increased in the infant or child who has extended fast or hypoglycemia could be caused by excess insulin, liver failure, or an IEM that interferes with ketone synthesis.
  - pH inappropriate for acid-base status because renal tubular acidosis can be a result of IEM.
- CBC.
  - Single or multiple failure of bone marrow cell lines
  - Macrocytosis (seen in disorders of energy metabolism, vitamin B_{12} and folate metabolism, and purine pyrimidine disorders)
- Liver enzymes for evidence of liver dysfunction.
  - Consider whether to fractionate bilirubin.
  - Consider testing prothrombin time and ammonia because they are true measures of liver function, not just liver inflammation.
- Evidence of pancreatitis.
- Consider testing creatine phosphokinase that could be evidence of rhabdomyolysis.
- Consider echocardiogram for cardiomyopathy (especially hypertrophic and arrhythmogenic right ventricular dysplasia).
- Hypsarrhythmia in neonate, triphasic waves, or any electroencephalogram described as having abnormal background.

Focused Testing for IEMs

- If not already done and if clinically indicated, check for hyperammonemia.
- Lactate and pyruvate.
- Blood amino acids.
- Organic acids.
- ACP.
- Carnitine total and free.
- Mucopolysaccharides or glycosaminoglycans in urine.

Special Considerations in Biochemical Evaluation

- Begin with more general metabolic tests.
- Testing for biochemical analytes is guided by clinical presentation.
- Like testing for toxins, the yield for specific biochemical (analyte) testing varies with the presentation.
- Use specific tests as indicated by presentation and initial testing.
- For the symptomatic patient, investigation begins by a careful examination of routine metabolic studies followed by specific studies.
  - Plan special studies with the genetics team, but initial testing should typically start before consultation.
- For the patient with a developmental disability who is not acutely ill, examine CBC, electrolytes, and liver function test results for indication to further studies.
- There is not necessarily any physical finding in patients with macrocytic anemia, renal tubular or metabolic acidosis, or liver dysfunction.
- For the acutely ill patient, inappropriately low ketosis is an important clue that can be detected by urinalysis.
- Ammonia.
  - Check in any patient with acutely altered mental status or acute ataxia.
  - Consider in a neonate with suspected sepsis; **Table 2** lists cautions about collection and handling.
- Lactate.
  - In the acutely ill patient or patient with hypotonia, consider testing lactate levels.
  - Lactate is also sensitive to collection and handling and levels can change in minutes.
- Biochemical studies of the patient with ammonia level 100× the upper limit of reference range is highly likely to identify a disorder of the urea cycle.
- Plasma amino acids (PAAs) in a patient with nonspecific developmental disability will have low yield compared with studies such as comparative genome hybridization.
- Total cost of testing the commonly measured analytes is a small fraction of the cost for care of the acutely ill patient or child with a neurodevelopmental disability.
- Biochemical testing in IEM patients who are not expected to survive.
  - Risk that future offspring in the family may be affected
  - Risk that an already living relative could be affected without having experienced symptoms

Table 2. Specific Metabolic Testing

Test	Description
Ammonia Typically green-topped tube (do not use ammonia heparin tube), free-flowing and placed on ice and hand carried to laboratory. However, each institution's laboratory has specific instructions.	Hyperammonemia is not evident on physical examination. Most accurate if collected without a tourniquet and couriered immediately to laboratory on ice because levels rise in the test tube until the sample is spun. Levels near or above 200 (sometimes 150) mcmol/L cause brain cell dysfunction and may cause cerebral edema; brain damage is universal and typically irreversible after 3 days of ammonia at levels >200 mcmol/L. Urea cycle defects may cause levels in the thousands of micromoles per liter. Hyperammonemia is an emergency; dialysis may be needed urgently, and specific drugs are available for "chemical dialysis." Although ideally collected properly, if an inappropriately collected level is normal, it excludes hyperammonemia as cause of coma; if it is markedly elevated, it is unlikely to be artifact, and if it is mildly elevated, an immediate repeat sample collected properly should clarify the situation because ammonia does not change rapidly without specific therapy. The level of ammonia will not necessarily distinguish urea cycle defects from organic acidemias, although the latter are more often associated with metabolic acidosis and an elevated anion gap.
Lactate (and pyruvate) Ideally special tube that hydrolyzes all protein, free-flowing and placed on ice and hand carried to laboratory. However, each laboratory has specific instructions.	Exquisitely sensitive to conditions of the patient and of the sample collection; lactate levels can change in minutes with changes in blood pressure and perfusion and with changes in IV glucose. Normal values are available for fasting and resting individuals. Lactate levels are useful in the emergency setting and elevations out of proportion to clinical status may provide clues to many IEMs. Lactate to pyruvate ratio is altered in some patients with mitochondrial disease, in the same direction as the alteration of the ratio in hypoxia or hypoperfusion. Lactate levels should always be collected and handled properly.
Blood AA Typically written PAA (green top), but some laboratories prefer serum (red or tiger top).	Laboratories that perform the test will have preference for plasma or serum; however, if your sample is not of the preferred type, contact the biochemical laboratory directly because they will typically be able to analyze the sample. Most laboratories also can perform the test on a sample smaller than that routinely requested for adults. Testing may also be done in some laboratories on filter paper. AAs can also be tested in other body fluids, most commonly urine and CSF, but metabolic autopsy testing can be done on vitreous of the eye or on renal papilla. AAs are conserved (reabsorbed) in the kidney so that blood analysis is useful for most conditions, but UAA analysis is key to diagnosis of conditions in which dysfunction of renal absorption of AA is the disorder. Laboratories will provide not only an interpretation but also the specific levels; an intermediary laboratory often will provide only the interpretation. The specific levels are needed to calculate the ratio of alanine to lysine, useful in evaluation of disorders of energy metabolism.

Table 2 (*continued*)

Test	Description
OA Typically written UOA; typically a random sample	Typically measured in urine because most OAs are toxic compounds that are poorly reabsorbed by the renal tubule, but some laboratories can perform limited testing on blood in anuric patients. Laboratories can typically test small samples. For acutely ill patients, samples are ideally collected at presentation before any therapies that affect metabolism.
ACP Most laboratories request green top for plasma; some prefer serum (red or tiger top), and some can analyze filter paper.	An analysis of markers that indicate what compounds are bound to carnitine. Not the same as a "carnitine profile." This is the preferred test for diagnosis of most disorders of fatty acid oxidation and is useful in many organic acidemias. For acutely ill patients, ideally collected at presentation before any therapies that affect metabolism. Often analyzed using the same methods that are used in newborn screening, but normal newborn screening does not substitute for ACP analysis in the symptomatic patient.
Carnitine total and free Most laboratories request green top for plasma; some prefer serum (red or tiger top), and some can analyze filter paper.	A measurement of the levels of free carnitine (that which is available for transport of fatty acids into the mitochondria) and of bound carnitine. Not the same as ACP. Particularly useful for diagnosis of disorders of carnitine transport and secondarily abnormal in many fatty acid oxidation disorders, organic acidemias, and some nutritional states.
Neurotransmitters Typically CSF; *requires special handling*	Some neurotransmitters can be measured in blood or urine, but certain conditions can only be identified by analysis of CSF. There is a rostrocaudal gradient of levels of the neurotransmitters in the CSF and, therefore, for results to be interpretable, the laboratory requires that the sample for neurotransmitters be collected in special tubes available from the laboratory and that the sample collection begin with the first drop of fluid—before measurement of pressure or collection of fluid for culture (the "special" tubes are also needed to prevent oxidation of some metabolites). CSF analysis for neurotransmitters, therefore, requires anticipation of collection and collaboration with appropriate specialists and with the local and reference laboratories.

Table 2 (*continued*)

Test	Description
UMPS Spot urine typically requested; first morning sample is preferred but not required.	The test for MPS. In Hurler or Hunter syndrome and other dysmorphic conditions, it can help to guide specific choice of enzyme or DNA testing. More controversial is the use of the test for screening patients with nonspecific developmental disability, including ASD. However, Sanfilippo syndrome is an MPS that yields no coarse features for the first decade or more and no skeletal problems; it presents as nonspecific developmental disability and classic ASD and is fatal; genetic counseling is indicated for affected families. Ideally, for UMPS testing, send to a laboratory that will fractionate the mucopolysaccharides if the screening result is positive, to avoid family stress by requesting follow-up sample.
CDG Serum is the sample typically used for screening (red or tiger top).	Evaluation of the level of protein glycosylation is a screening test for CDGs. The extreme complexity and variety of glycosylation of proteins limits the sensitivity of screening, so false-negative results are possible, and false-positive results can occur, especially in liver disease. The screening test is nevertheless powerful and can be diagnostic in some cases. The original and more limited test is immunoelectrophoresis of transferrin, with simple N-linked sugars; it is important to distinguish the test for CDG from the test of transferrin glycosylation to monitor alcoholic liver disease. The more powerful screen examines both transferrin and apolipoprotein E, which has O-linked glycosylation. Still more sensitive and specific is tandem mass spectroscopy to examine a broad range of proteins with more varied combinations of carbohydrates.

Abbreviations: AA, amino acid; ACP, acylcarnitine profile; ASD, autism spectrum disorder; CDG, congenital disorder of glycosylation; CSF, cerebrospinal fluid; IEM, inborn error of metabolism; IV, intravenous; MPS, mucopolysaccharidosis; OA, organic acid; PAA, plasma amino acid; UAA, urine amino acid; UMPS, urine mucopolysaccharide; UOA, urine organic acid.

- Metabolic autopsy
  - Performed if the suspicion of an IEM is sufficiently high.
  - Performed only if necessary resources are available through pathology, including immediate (ideally ≤1 hour of death) collection and preservation of tissue samples at -70°C to -80°C (-94°F to -112°F).
  - Samples could then be used for enzyme assays indicated by tests of analytes collected before or at the time of death.
  - Any discussion of the option of "metabolic autopsy" must include the possible costs.
    - Testing of stored samples that might be ordered after death is usually not covered by insurers.
  - A lower-cost, limited screening option is to send a sample on filter paper to a laboratory that analyzes amino acids and an ACP on autopsy sample.
  - Some laboratories will accept and bank a sample of DNA for the family's future DNA testing.

IMAGING

- No single imaging test is specific to the diagnosis of an IEM, but imaging is a critical part of diagnostic evaluation and monitoring in many categories of IEMs.
- Echocardiography.
  - To identify a cardiomyopathy that should suggest the possibility of disorders of fatty acid oxidation or carnitine, glycogen storage, or disorders of mitochondrial energy metabolism
  - To monitor individuals with some of these conditions, certain organic acidemias, and lysosomal storage disorders
- Skeletal radiographs and survey.
  - Views of the lateral spine are key to identifying dysostosis multiplex.
  - Can narrow the diagnosis to a specific category of IEM in a child with
    - Slowing growth who shows dysostosis multiplex of certain lysosomal storage disorders
    - Stippling of the epiphyses of certain peroxisomal disorders
- Magnetic resonance imaging (MRI).
  - Can show changes in basal ganglial white matter of Leigh disease, suggesting one of the many disorders of mitochondrial energy metabolism.
  - Can show white matter changes in the occipital region, suggesting the peroxisomal disorder adrenal leukodystrophy.
  - Examine MRI for white matter disease, including stroke and periventricular leukomalacia in absence of clear history of asphyxia or clot.
  - Consider magnetic resonance spectroscopy for lactate, creatine, or other appropriate metabolites.
- When imaging requires special preparation (eg, sedation for MRI), consider whether additional studies can be done at the same time.

DIAGNOSTIC PROCEDURES

- Lumbar puncture
  - May be necessary for examining
    - Amino acids
    - Neurotransmitters
    - Other analytes
- Biopsy
  - Relatively simple skin biopsy can be done for histology or for culture of fibroblasts for biochemical testing.
  - Special stains and electron microscopy are likely to be helpful.
  - Include pathologist in the discussion of differential diagnosis to ensure appropriate sample handling.
  - Biopsies of muscle and liver can be especially useful for histology, histochemistry, and electron microscopy as well as enzyme assays and other biochemical testing.
- Functional studies
  - Electroencephalography
  - Nerve conduction or electromyogram
- Specific physiologic challenges
  - May be useful or necessary for clinical diagnosis and management.
  - Challenge by diet, exercise, fasting, or specific medications.
  - Challenges can be dangerous.
  - Some challenges can be performed on an outpatient basis.
  - Some should be done only in an intensive care unit with secure vascular access.
  - Should be undertaken in consultation with a specialist.
  - In many cases there may be overlap between the evaluation for endocrine and IEM conditions that can cause a specific presentation, especially when the presentation includes hypoglycemia.

- If medium-chain acyl coenzyme A dehydrogenase deficiency is on the differential diagnosis, a child should not undergo fasting until an ACP has shown no evidence of that condition.
- The action of glucagon is to increase lipolysis, and any child with a disorder of fatty acid oxidation will experience worsening symptoms if glucagon is given as part of a challenge.

CLASSIFICATION

- IEMs are classified according to the metabolic pathways.
  - Some experts classify IEMs according to whether they cause acute toxicity or chronic disease.
- For the primary care physician, it may be most appropriate to consider IEMs, as they are most likely to present.
- Acutely ill patient (shock, possible septicemia, altered mental status).
  - Inborn errors of the amino acids, organic acids, the urea cycle, fatty acid oxidation, mitochondrial metabolism, and several others may cause severe symptoms with gradual or sudden onset.
  - Suspect when
    - Altered mental status is apparent.
    - Acid-base status is out of proportion to the physical findings.
    - Prior episodes of dehydration with intercurrent illnesses.
    - When poisoning is suspected, unless a specific ingestion is known or suspected.
  - Infection or non-accidental trauma does not exclude an IEM.
  - Examine ammonia levels and liver functions to avoid missing important clues to a diagnosis.
  - Check plasma ammonia in any neonate suspected of sepsis with gastrointestinal symptoms or altered consciousness.
  - While evaluation begins, remove all protein and lipids and all sugars except glucose from nutritional management.
  - Provide adequate glucose to stop catabolism.
  - Consider measuring lactate and pyruvate.
- Dysmorphic features and malformations.
  - Classic dysmorphic syndromes resulting from IEMs include
    - Smith-Lemli-Opitz syndrome
      - Failure of cholesterol synthesis (small size, feeding disorders, characteristic facial features with cleft soft palate, heart defect, pyloric stenosis, syndactyly of the second and third toes, extra-axial polydactyly, hypospadias)
    - Zellweger syndrome
      - Failure of biogenesis of peroxisomes (cerebrohepatorenal syndrome with facial features including high forehead and flat face, liver and renal cysts, and extremely low tone)
  - Other conditions involve brain malformations, especially disorders of mitochondrial energy metabolism and congenital disorders of glycosylation.
  - Many mucopolysaccharidoses have characteristic coarse features of face and progressive skeletal dystrophy.
  - Patients with some chromosomal abnormalities are at increased risk for an IEM.
    - For example, patients with contiguous gene deletions may have only one carrier parent for an IEM if the gene is in the deleted region.
  - Patients with uniparental isodisomy are homozygous for all genes on the affected chromosome and have an IEM if the parent providing that chromosome was a carrier.
- Failure to thrive with or without vomiting.
  - Consider an IEM if
    - Vomiting persists despite management of reflux.
    - There is alteration of development, neurologic examination, or neurodevelopment.
  - Brain growth and neurodevelopment in children with nutritional failure to thrive are usually preserved unless malnutrition is severe.
  - Examine acid-base status.
  - Check liver functions and CBC.
  - Examine the MCV in the CBC
  - Begin evaluation for an IEM with blood amino acids (PAA or serum amino acid [SAA]), UOA, ACP, and total and free carnitine.
- Abnormal neurologic system.
  - Examples include
    - Early hypertonia
    - Late hypotonia
    - Episodic or progressive ataxia or other movement disorder
    - Atypical or unresponsive seizures
    - Episodic altered consciousness
  - Examine acid-base status and liver function.
  - Assess for macrocytosis and collect blood amino acids (PAA or SAA), UOA, and ACP.
  - Measure blood ammonia in patients with acutely altered mental status or acute ataxia.
  - Ophthalmologic examination for cataracts or retinopathy.

- When collecting CSF, examine lactate and amino acids and consider measuring neurotransmitters and other metabolites of IEMs.
- To evaluate the cause of seizures, collect blood glucose and PAA immediately before a lumbar puncture so that the ratio of CSF to plasma glucose and glycine can be evaluated.
- When planning an MRI, ask for magnetic resonance spectroscopy to examine lactate for clues of inborn errors of energy metabolism.

- Intellectual disability and ASD (especially with slowing development, developmental plateau, and regression).
  - Many conditions that cause regression are IEMs, including some that are fatal and autosomal recessive.
  - History and examination can help distinguish those who need more aggressive evaluation.
  - No physical findings exclude the presence of acidosis, liver disease, or macrocytosis.
  - Basic studies of electrolytes, liver health, and CBC are appropriate for all children presenting with intellectual disability unless clear cause is known.
  - More specific studies for IEM in the absence of regression or other clues on history or examination (eg, hypotonia) vary.
    - Many experts urge that the following levels be evaluated in all patients with intellectual disability or ASD:
      - Blood amino acids (for phenylketonuria [PKU] and homocystinuria, which could have been missed by newborn screen)
      - Urine mucopolysaccharides (for Sanfilippo syndrome)
- Single or multiple organ failure.
  - Potentially reversible conditions.
    - Renal failure from Fabry disease
    - Liver failure from tyrosinemia
    - Cardiomyopathy from fatty acid oxidation or Pompe disease
  - Conditions less responsive to therapy.
    - Liver or bone marrow failure in children with mitochondrial disease
  - Awareness of the diagnosis can help with management.
    - Avoid valproic acid when treating children with seizures from an IEM.
    - Infection may be the trigger leading to the presentation of an IEM.
    - Some IEMs include immune deficiency that can increase the risk for infections.
  - Evaluation of a child with single or multiple organ failure typically includes testing for IEMs known to cause the specific presentation.
    - In general, testing includes the evaluation of blood amino acids, UOA, ACP, and carnitine (total and free), in addition to any disease-specific testing.
- Stroke or clotting disturbance.
  - Thrombotic stroke is standard presentation of classic homocystinuria resulting from cystathionine β-synthase deficiency.
  - Newborn screening misses up to half the patients with classic homocystinuria and most with variant types.
  - Some patients may have marfanoid habitus or a history of developmental disability; others have no signs or symptoms of an IEM.
  - Total homocysteine, blood amino acids, and UOA should be included with studies for other genetic causes.
  - Consider the possibility that the child has experienced a stroke-like episode of MELAS syndrome (**m**itochondrial **e**ncephalomyopathy, **l**actic **a**cidosis, and **s**troke-like episodes).
  - Include Fabry disease and congenital disorders of glycosylation in the differential diagnosis.

TREATMENT APPROACH

- Many IEMs have specific treatments that can reduce or even prevent disability or death.
- The first step to managing an IEM in the pediatric and pediatric specialty practice is making the diagnosis so that appropriate treatment can be offered.
- The diagnosis can only be made when IEMs are appropriately suspected and testing initiated.
- The stakes can be high for emergency recognition of IEM (eg, in a child with overwhelming acidosis or a child in a coma that proves to be caused by hyperammonemia).
- The primary care physician or nongenetic pediatric specialist typically works with a geneticist in the management of IEM.
- Management is often initiated in the acutely ill patient by excluding potentially harmful dietary components and by providing glucose in amounts sufficient to prevent catabolism.
- Patients who have an IEM, when stabilized and in the chronic phase of management, typically are not hospitalized because of the underlying IEM.

- Rather, a viral illness, fasting, or another disorder will tip the balance and cause a metabolic crisis unless the child is treated promptly.
- Primary care physicians, therefore, are on the front lines of management of these children.
- Maintaining vaccination schedules as recommended by the American Academy of Pediatrics and obtaining annual influenza (killed) vaccinations in the affected child and family members are simple yet critically important aspects of pediatric care.

SPECIFIC TREATMENTS

- Some conditions that, in the recent past, were untreatable and fatal (eg, Pompe disease) can now be treated with enzyme infusions that can reverse some symptoms and prevent further injury.
- Anticipatory guidance is critical for managing all IEMs.
- Genetic counseling is important for families and for the patients themselves when they consider future reproductive risks.
- Collaboration is the basis of the specific management, especially for conditions for which there are risks for metabolic crises.
- Specific management is available for many IEMs.
  - Maple syrup urine disease
    - Branched chain amino acid–restricted diet
  - Vitamin B_6-responsive seizures
    - Provision of cofactor
  - PKU
    - Some respond to therapy with the cofactor biopterin.
    - Patients with poor compliance in late childhood and teen years are at risk for progressive white matter disease of the brain.
    - Elevated phenylalanine is a teratogen; young women with poorly controlled PKU will have offspring with intellectual disabilities and malformations.
- For other IEMs, the specific current treatment consists solely or primarily of supportive, symptomatic management.
- Patients and families often wish to participate in experimental therapies, especially for conditions that are fatal and have no proven effective therapy.
- Emergency care.
  - The metabolic expert should provide instructions for chronic care and any emergency.
  - Sometimes there will be specific adjustment of care if a child is acutely ill, and supportive care will be appropriate in all cases—even where there are limitations for end-of-life care.
  - In an acute emergency, after the ABCs (**a**irway, **b**reathing, **c**irculation), the most important part of care for the child with an IEM is usually prevention of catabolism.
  - Emergency physician must distinguish between concerns for catabolism and blood glucose levels.
    - Except for certain glycogen storage disorders, the pathophysiology that can present with acute crisis is such that blood glucose remains within reference range until metabolic balance decompensates past a critical point.
  - The metabolic specialist's instructions for rate of intravenous (IV) glucose administration should be followed when the patient is unable to tolerate enteral intake, regardless of the blood glucose level.
    - Then remain on IV glucose until enteral intake is tolerated.

WHEN TO ADMIT

- Joint decision of the primary care physician, family, and specialists
- If home management is not sufficient to keep the child out of crisis (eg, child cannot maintain anabolism)
- As required for invasive evaluation

WHEN TO REFER

- Refer, or at least discuss the possibility, when there are symptoms and signs that suggest IEM, especially with any of the following presentations:
  - Neurodevelopmental abnormalities, especially acute altered mental status and recurrent or intermittent symptoms or progression, hypotonia >1 year, or a movement disorder.
  - Acidosis out of proportion to systemic illness.
  - Hypoketosis for the state of nutrition and, especially, hypoglycemia.
  - Cardiomyopathy, liver failure, failure to thrive, and renal tubular acidosis.
  - Positive newborn screening result for an IEM.
  - Family history of IEM.
  - IEM is suspected for any other reason.
  - No other cause of the presenting problem is found that is unequivocally the primary underlying cause.
- In some cases, especially if the child is critically ill and certainly if there is regression, referral should be directly to a geneticist who is an expert in IEMs.

- When a child is stable, it may be appropriate for the primary care physician to work with another specialist, such as a gastrointestinal or neurology specialist, to consider whether a genetics or metabolic referral is warranted.

FOLLOW-UP

- Management is a collaborative effort with the metabolic specialist, geneticist, and other appropriate specialists.
- Transition to adult care.
  - An issue for all pediatric patients with chronic disease.
  - In many cases the genetics team will remain constant.

COMPLICATIONS

- Frequently include
  - Neurologic dysfunction (central and peripheral)
  - Cardiomyopathies
  - Liver disease or liver failure
  - Growth failure
  - Intestinal dysfunction
  - Deafness
  - Eye disease, including cataracts and retinopathy
  - Muscle disease, including rhabdomyolysis
  - Single or multiple endocrine gland failures
  - Birth defects
- An important complication is the effect on the family.
  - For many conditions lifesaving therapy involves substantial modification of ordinary living.
- IEMs affect decisions about whether to have other children.
- There may be complicated interactions with the broader family for support for the affected child and for disclosure of genetic risks.

PROGNOSIS

- The prognosis varies with the specific condition.
  - For some IEMs, response is excellent and the only "complication" is the need to remember that failure to continue therapy is life-threatening (eg, biotinidase deficiency).
  - For others, available therapy is limited and complications and eventual death are not preventable.
- Severe neurologic or other injury may have already resulted before diagnosis.
  - Particularly with some disorders of fatty acid oxidation and organic acidurias
- Preventable morbidity from treatable conditions justifies newborn screening when feasible.

PREVENTION

- For the affected individual.
- The goal is to prevent medical and developmental complications by use of appropriate management.
- Avoidance of known risks or triggers, including drugs with adverse effects on relevant pathways.
  - Mitochondrial metabolism
  - Porphyria pathways
  - Synthesis of cholesterol
- Standard health care is critical, including use of all relevant vaccines.
  - For patients with conditions that include metabolic crisis as part of the presentation, use of killed vaccine for patient and family members is recommended.
  - Only a few of the IEMs have immune deficiency; the risk for a family member inoculated with live virus to pass infection on to the affected individual must be considered.
- Recurrence risk within families is significant.
  - In all cases, family must be offered accurate information about the risk for recurrence.
  - In some cases, a living individual is at risk and needs to be offered evaluation and care.
  - Offer information in the context of genetic counseling that respects the individual's and family's beliefs and values.
  - When carrier or prenatal testing or other prenatal options are possible, offer relevant information, along with the opportunity to explore how to use such opportunities.
- The physician should mitigate any adverse effects of the IEM and its consequences on the individual's and family's function.
  - Supportive or habilitation services
  - Options to connect with other affected individuals, families, or support organizations

DEFINITION

- Microcephaly refers to a head size ≥2 standard deviations (SDs) below the mean (about the third percentile).
  - Norms based on age and sex.
  - Child may be neurologically typical, especially if very close to the third percentile curve.
  - Head size >3 SDs below the mean is probably associated with neurologic impairment.
  - Classified as
    - Primary microcephaly—genetic
    - Secondary microcephaly—environmental
    - Congenital versus acquired
    - Syndromic versus nonsyndromic
- Micrencephaly refers to having a small brain.
  - Leads to a small head size
- Compare with craniosynostosis—premature closure of sutures (with normal brain growth).
- Congenital microcephaly: present from birth.
- Acquired microcephaly: Head circumference does not grow as expected after birth.

HISTORY

- Medical history, including
  - Previous infections, such as meningitis
  - Results of neuroimaging studies
- Review of systems, including
  - Feeding difficulties
  - Seizures
- Family history
  - Construct a pedigree, noting genetic syndromes, miscarriages, and microcephaly.
  - Family history of small head size in context of normal development and neurologic examination describes asymptomatic familial microcephaly.
- Prenatal history
  - Explore potential toxin exposure (alcohol, drugs).
  - Review maternal health during pregnancy.
  - Review records and assess the likelihood of intrauterine infections.
  - Review records and assess the likelihood of placental insufficiency.
  - Discuss psychosocial factors, including history of prenatal care and maternal education.
- Developmental history
  - Include a chronology of developmental milestones.
  - Assess the child's current function and behavior.
  - Note any developmental regression.

PHYSICAL EXAMINATION

Vital Signs and Anthropomorphisms

- Measure stature, weight, and head circumference.
  - Perform these at each well-child visit, especially in first 3 years of life.
  - Measure head circumference with a flexible, non-stretchable tape.
    - Measure above the supraorbital ridges and across the occipital prominence.
    - This occipitofrontal circumference correlates with brain volume.
    - Consider repeating suspicious measurements yourself.
  - Plot measurements on standardized charts.
    - Centers for Disease Control and Prevention growth charts from 2000 include curves for the 3rd and 97th percentiles.
    - World Health Organization released new international growth charts for children 5 years and younger.
      - Applicability in clinical practice is under investigation.
    - For children >3 years, growth curves developed by Nellhaus were traditionally used.
    - Newer US charts from birth to 20 years have been published.
    - Adjust head circumference for preterm birth until ~2 years of age.
      - In neonates with birth weight <1,000 g, use corrected age until 3 years of age (or until growth has caught up to normal).
    - Use charts specific to special populations when indicated (eg, Down syndrome, Williams syndrome, achondroplasia, very low birth weight neonates).
  - Measuring over time allows early identification of when percentiles are crossed, even if measurements are still within reference ranges.
  - Disproportionately small head circumference, with respect to stature and weight, may indicate a central nervous system condition.
- Measure head circumferences of other family members as possible.
- Evaluate heart rate, respiratory rate, and blood pressure for Cushing triad (bradycardia, irregular respirations, hypertension).

Physical Examination

- Inspect and palpate skull, looking for asymmetry and bony ridges.
  - Bony ridges may suggest craniosynostosis.
- Examine for features of genetic conditions.
  - Characteristic facies (eg, Seckel syndrome, Down syndrome, de Lange syndrome)
  - Evidence of involvement of other organ systems, such as
    - Ocular abnormalities (eg, colobomas, cataracts)
    - Congenital heart disease
    - Genitourinary abnormalities (eg, cryptorchidism)
- Examine the skin.
  - Rash of intrauterine infection may be apparent.
- Examine for neurologic abnormalities indicative of potential central nervous system malformation.
  - Pupils, extraocular muscles, visual fields, smell, and cranial nerve functions.
  - Funduscopic examination for papilledema.
  - Assess for asymmetries, abnormalities in muscle tone, posture, strength, and reflexes.

DIFFERENTIAL DIAGNOSIS

- Microcephaly is a physical finding, not a diagnosis.
- Asymptomatic familial microcephaly.
  - Small head size in context of normal development, normal neurologic examination, and family history
- Genetic causes (primary microcephaly).
  - Small brain/abnormal brain development
    - Microcephaly vera ("true microcephaly")
      - Brain size usually 3 SDs below the mean.
      - Brain architecture grossly normal.
      - Patients almost always have intellectual disability but have otherwise unremarkable neurologic examination.
    - May see sloping forehead and prominent ears.
    - Microcephaly with severe neurologic impairment (seizures, spasticity, or global developmental delays)
      - More common than microcephaly vera.
      - Neuroimaging may identify abnormal brain architecture.
  - Genetic syndromes
    - Miller-Dieker syndrome (17p; deletion/mutation of *LIS1* gene)
      - Small smooth brain/lissencephaly, facial dysmorphism, severe intellectual disability
    - Seckel syndrome (multiple possible loci: 3q, 18, 14q; autosomal recessive)
      - Low birth weight, intrauterine growth restriction
      - Growth delays after birth resulting in short stature
      - Bird-headed appearance ("beak-like" protrusion of nose, abnormally large eyes, narrow face, malformed ears, small jaw)
      - Varying degrees of intellectual disability
    - Rubinstein-Taybi syndrome (22q, 16p; autosomal dominant; mutation in CREB binding protein)
      - Characteristic facial features, moderate to severe intellectual disability, broad thumbs and toes.
      - Other findings may include coloboma, cataract, congenital heart disease, renal abnormalities, and cryptorchidism.
    - Down (trisomy 21) syndrome
      - Distinct facial features, congenital heart anomalies, and growth retardation
    - Patau (trisomy 13) syndrome
    - de Lange syndrome (multiple possible loci: 5p, Xp, 10q; mutation in cohesin complex)
      - Growth retardation, hirsutism, and unusual facial features, such as synophrys and low anterior hairline.
      - Microcephaly is almost always present at birth.
    - Rett syndrome (X chromosome; mutation in gene encoding *MECP2*)
      - Condition of decelerating head growth toward second year of life, almost exclusively in females; most cases appear to be sporadic.
      - Developmental regression, autistic features, and unusual hand mannerisms (hand-wringing and hand-washing movements).
  - Metabolic disorders that may lead to deceleration of head growth in first year of life should be considered with
    - History of parental consanguinity
    - Episodic symptoms, such as vomiting and encephalopathy
    - Developmental regression

- Environmental causes (secondary microcephaly).
  - Intrauterine environment/perinatal time frame
    - Teratogens
    - Fetal alcohol syndrome
      - Intrauterine growth restriction
      - Small palpebral fissures, smooth philtrum, and thin upper lip
      - Heart and eye defects
      - Behavioral and cognitive deficits
    - Maternal metabolic disease
      - Untreated maternal phenylketonuria and hyperphenylalaninemia may produce findings similar to those of fetal alcohol syndrome: facial dysmorphism, intellectual disability, and heart defects.
    - Intrauterine infections (eg, TORCH [**t**oxoplasmosis, **o**ther agents, **r**ubella, **c**ytomegalovirus, and **h**erpes simplex])
    - Maternal health problems
    - Intrauterine irradiation
    - Hypoxic-ischemic encephalopathy
      - Severe perinatal asphyxia is an important cause of acquired microcephaly.
      - Typical head circumference at birth, but head growth decelerates.
      - May be detected as early as 6 weeks of age; these infants develop significant neuromotor and cognitive deficits.
  - Infections
    - Meningitis
  - Severe malnutrition
  - Traumatic brain injury and abusive head trauma
- Craniosynostosis (multiple sutures; problem of skull, not brain).
  - Head circumference may be small at birth, or head growth may abruptly cease during infancy.
  - Asymmetric skull with bony ridging in the areas of fused sutures.
  - Increased intracranial pressure may be present.

LABORATORY EVALUATION

- Laboratory evaluation is guided by clinical suspicion.
- In children with possible intrauterine infection
  - Test for perinatal infections.
    - Toxoplasmosis
    - Rubella
    - Cytomegalovirus
    - Syphilis
    - HIV
    - Herpes
  - Ophthalmologic and audiologic evaluations.
- If a genetic syndrome is suspected, perform a focused evaluation, consulting experts in genetics as needed.
  - Karyotype
  - Genetic testing is available for
    - Miller-Dieker syndrome
    - Rett syndrome
  - For children with microcephaly and dysmorphic features
    - Array comparative genomic hybridization testing
- Metabolic testing.
  - Usually not recommended in an asymptomatic newborn with microcephaly.
  - Consider for postnatal-onset microcephaly, especially with history of parental consanguinity, episodic symptoms, or developmental delay or regression.

IMAGING

- Neuroimaging most useful in cases of severe microcephaly (>3 SDs below the mean)
- Neuroimaging may help to identify abnormal brain architecture, such as
  - Holoprosencephaly
  - Lissencephaly
  - Schizencephaly
  - Pachygyria
  - Polymicrogyria
  - Heterotopias
  - Midline defects (agenesis of corpus callosum)
- Imaging modalities include
  - Magnetic resonance imaging (MRI)
    - Use when the following conditions are suspected:
      - Gray and white matter disease
      - Migration defects, such as lissencephaly, pachygyria, and polymicrogyria
    - MRI is limited in its ability to study bone and calcifications.
  - Computed tomography
    - Use when the following conditions are suspected:
      - Intracranial calcifications from intrauterine infections
      - Skull abnormalities, as seen with premature fusion of cranial sutures
      - Ventricular system abnormalities

- Radiography of the skull
  - Can demonstrate intracranial calcifications.
  - Can show characteristic bone findings in craniosynostosis.
  - Cannot detect abnormalities in brain structure.
- Ultrasonography
  - Useful in infants with open fontanels

TREATMENT APPROACH

- Treatment is largely supportive, with targeted therapies to address functional disabilities.
- Refer to early intervention and special education services as needed.

SPECIFIC TREATMENT

- Children with microcephaly may have multiple medical issues; treatments depend on the individual.
- There is a reported risk of cardiac arrhythmia with use of succinylcholine in children with Rubinstein-Taybi syndrome.

WHEN TO REFER

- Head circumference >2 SDs below the mean (especially >3 SDs)
- Deceleration of head growth
- Dysmorphic features
- Abnormal neurologic examination and development
- Regression in motor, language, and social skills
- Seizures
- Suspected craniosynostosis

WHEN TO ADMIT

- Signs of increased intracranial pressure
- Mental status changes

FOLLOW-UP

- Children with microcephaly may require close follow-up for developmental issues.

PREVENTION

- Prevention.
  - Appropriate prenatal care
  - Maternal education and nutrition
  - Avoidance of teratogenic substances
  - Screening for intrauterine infections
  - Management of maternal health conditions
- Genetic counseling may be offered to parents if genetic disorders are identified.

Mononucleosis and Epstein-Barr Infections

DEFINITION

- Epstein-Barr virus (EBV) is a member of the herpesvirus group.
- EBV infections can produce infectious mononucleosis.

SIGNS AND SYMPTOMS

- In childhood, EBV infection is usually inapparent clinically or characterized by a nonspecific, uncomplicated episode of upper respiratory tract infection or pharyngitis.
- The incubation period is 2–6 weeks (usually 20–30 days).
- Classic signs of infectious mononucleosis include
  - Fever, severe
  - Sore throat
  - Lymphadenopathy
- This constellation of symptoms and signs may be preceded by vague symptoms of
  - Fatigue
  - Malaise
  - Anorexia
- Infectious mononucleosis is the result of a systemic viral infection.
  - Every organ system may be involved.
- Clinical manifestations compatible with infectious mononucleosis include
  - Fever
    - Usually not >39.5°C (103°F)
  - Lymphadenopathy
    - Most striking feature of the illness.
    - Can be limited to the cervical nodes.
    - Can involve virtually all lymph node groups.
    - Posterior cervical adenopathy is frequently noted.
    - The lymph nodes are not usually intensely tender and rarely demonstrate other signs of inflammation.
    - However, palpation of the neck can elicit moderate to severe pain as reflection of the intense inflammation of the pharynx and surrounding tissue.
  - Sore throat
    - Can be excruciating
    - Frequently accompanied by tonsillar exudate and a palatal enanthema or a grayish-white necrosis of the tonsillar surfaces in adolescents
  - Splenomegaly
    - Some patients do not have any palpable splenic enlargement.
  - Hepatomegaly
    - Liver enzyme levels are elevated in virtually all patients.
    - Jaundice is infrequent.
  - Rhinitis, cough
  - Rash
    - In ~20% of children
    - Erythematous
    - Petechial
    - Erythema multiforme-like
    - Urticarial
    - Scarlatiniform
    - In 70%–90% of young adult patients and in a proportion of younger children treated with ampicillin or amoxicillin during acute EBV infection
    - Can appear after the medication has been discontinued
  - Abdominal pain
  - Upper eyelid edema (Hoagland sign)
    - In ~25%
- Severity of illness is extremely variable.
  - Some individuals may have relatively few manifestations of infection.
  - Others will demonstrate virtually all symptoms.
- Acute clinical manifestations last ~2–3 weeks.
  - Peak involvement during the second week

DIFFERENTIAL DIAGNOSIS

- Massive enlargement of the spleen suggests an alternative diagnosis.
- EBV-negative infectious mononucleosis.
  - Symptoms similar to those of EBV infection can be produced by
    - Rubella
    - Hepatitis A
    - Toxoplasmosis
    - Cytomegalovirus (CMV)
    - Human herpesvirus 6
    - Adenovirus infections
    - Systemic lupus erythematosus
    - Drug reactions
  - Negative EBV titers and heterophil antibody responses strongly suggest one of these other agents or conditions as the cause.
  - In hepatitis A
    - Heterophile test can give a false-positive result.
    - Liver enzyme levels generally are much more elevated than those seen with EBV infectious mononucleosis.

  - Results of serologic tests for hepatitis A will be positive.
- Rubella titers in rubella infection will be positive.
- CMV generally does not produce pharyngitis with CMV-induced mononucleosis.
  - Serology can be difficult to interpret because CMV immunoglobulin M (IgM) can be detected in reactivation.

- Illnesses that mimic infectious mononucleosis but lack serologic confirmation of EBV should be classified as heterophil-negative infectious mononucleosis rather than atypical mononucleosis.
  - Cause of most of these cases is unknown.

DIAGNOSTIC APPROACH

- Diagnosed by the presence of a triad of findings
  - Clinical
  - Hematologic
  - Serologic
- Minimal hematologic features should include
  - Lymphocytosis of ≥50% of all leukocytes
  - Atypical lymphocyte count of ≥10% of all leukocytes

LABORATORY FINDINGS

- General laboratory findings usually include a decrease in the number of granulocytes and platelets.
- Paul-Bunnell antibodies are not EBV specific but are heterophilic IgM produced by EBV-infected B cells and react with horse, sheep, and bovine erythrocytes but not with guinea pig kidney cells. These are the basis for most rapid "mono" tests.
  - Will be present in ≤50% of children <4 years.
  - Among school-aged children and young adults, detectable 80%–90% of the time during the second week of clinical illness.
  - Heterophil response will be brief and minimal, particularly in young children, or will occur late in the illness.
    - Often shows negative results early in the course of the illness
  - Commercial diagnostic kits rely on differential red blood cell adsorption to detect the heterophile antibody.
    - Readily available and easy to use in a physician's office.
    - 96%–99% sensitive when the antibody is present.
    - Give a result in 2 minutes.
    - False-positive results can occur in cases of
      - Rubella
      - Hepatitis
      - Serum sickness
      - Drug reactions
      - Systemic lupus erythematosus
      - Improper use of the kit
      - Inaccurate interpretation of the agglutination reaction
    - Magnitude of the heterophile antibody titer does not correlate with clinical severity.
    - Repeat testing, once a positive test result is obtained, provides no additional information beyond that gained from the clinical assessment.
- Heterophile tests can remain positive for years and are not useful in testing after the initial episode of mononucleosis if similar symptoms reappear.
- If heterophile test results are negative and EBV infection is strongly suspected, confirmation of EBV infection should be sought by other serologic tests.
- Patients who have negative heterophile test results will have antibodies against specific components of the virus if EBV is the cause of illness.
- A variety of antibodies directed against various EBV components can be detected.
- 4 different antibodies define the EBV serologic profile (**Table 1**).
  - IgM antibody to viral capsid antigen (VCA-IgM).
  - IgG antibody to viral capsid antigen (VCA-IgG).
  - IgG antibody to early antigen (anti-EA).
  - IgG antibody to Epstein-Barr nuclear antigens (anti-EBNA).
  - Not all laboratories test for anti-EA, which may be detected in 2 patterns: diffuse and restricted.
    - The clinical implication of diffuse or restricted is not clear for mononucleosis but is used to follow some EBV-induced lymphoma patients.
    - These EBV-specific antibodies appear in patients who have or have had a primary EBV infection.
  - The pattern of antibody responses can help determine the relative onset of an individual's EBV infection.
  - In most cases, an individual develops a VCA-IgM antibody (or VCA-IgG antibody) response in the acute period (first 2–3 weeks) after an EBV acquisition.
  - IgG antibodies to VCA persist for life.

Table 1. Interpretation of Epstein-Barr Virus Serology

	Heterophile Antibody	Epstein-Barr Virus Specific Antibodies			
		VCA-IgM	VCA-IgG	EA	EBNA
No or first week of infection	–	–	–	–	–
Acute infection	+/–	+	+ (>1:320)	+/–	–
Past infection	–	–	+ (1:80–1:160)	+/–	+

Note: Other patterns may occur in an individual patient; this profile is for a typical individual.

Abbreviations: EA, early antigen; EBNA, Epstein-Barr nuclear antigen; VAC-IgG, IgG antibody to viral capsid antigen; VCA-IgM, IgM antibody to viral capsid antigen.

Derived from Sumaya CV, Ench Y. Epstein-Barr virus infectious mononucleosis in children. I. Clinical and general laboratory findings. *Pediatrics*. 1985;75(6):1003–1010.

- VCA-IgM tends to disappear in 2–3 months.
- Height of the VCA-IgG response decreases as the acute infection resolves.
  - — Serial measurements of antibody titers are not clinically beneficial.
- Anti-EA response peaks at 3–4 weeks into the illness.
  - — Initially thought to persist only for several months.
  - — In the past, was considered a good marker for an acute or recent infection.
  - — Recent evidence suggests that anti-EA response may persist for years in some children and may not develop at all in others.
- Anti-EBNA antibody response usually appears several weeks to months after a primary infection.
  - — A marker for past or convalescent infection
  - — Must be interpreted in light of the clinical situation
    - A few children develop this response in the late stages of the acute phase of their infection.
    - 10%–20% may never develop detectable EBNA.

- Children who acquire EBV infections typically develop antibodies in the same sequential pattern.
  - Not all patients follow the same pattern.
- Clinical judgment remains important in the interpretation of such findings.
- Interlaboratory variability in results of EBV antibody testing has been observed.
  - Reliability of tests is suspect in some cases.
  - If heterophile test and EBV-specific serologic results are negative, non-EBV causes for infectious mononucleosis-like illness should be suspected.

TREATMENT APPROACH

- Most patients who have infectious mononucleosis recover uneventfully.
- Physicians need do little except
  - Establish the diagnosis.
  - Explain the nature of the illness.
  - Reassure the patient and parents.
- No specific therapy is indicated.
- Patients should rest to the extent that they believe necessary.
- As long as the patient can consume adequate amounts of fluids and calories, hospitalization is unnecessary.
- To minimize the danger of splenic rupture, ambulatory patients should avoid strenuous physical exercise and contact sports for at least 1 month or until the spleen is no longer palpable.
- Patients who have a late-onset heterophile antibody response appear to have a prolonged convalescence.
- Accounts are increasing (although still rare) of infectious mononucleosis episodes that are severe or fatal or result in significant long-lasting problems.
  - Most of these patients had some form of immunologic abnormality.
    - — X-linked lymphoproliferative syndrome
    - — Renal or bone marrow transplant
    - — Chédiak-Higashi syndrome
  - Definitive management of these patients remains unclear.

SPECIFIC TREATMENTS

Corticosteroids

- Corticosteroids are of unproved value in treating this illness.
  - Should not be used routinely merely to make the patient feel better

- Controlled studies documenting efficacy are lacking.
- Most clinicians believe that their use is justified in treating
  - Severe hemolytic anemia
  - Significant airway obstruction secondary to tonsillar hypertrophy
  - Thrombocytopenia
- Some authorities suggest using corticosteroids if neurologic involvement is significant.
  - Proof of efficacy is not available.
- High-dose, short-term courses of steroids have been used with dramatic improvement typically noted over 24–72 hours.
  - Dexamethasone: 0.25 mg/kg every 6 hours
  - Methylprednisolone: 1 mg/kg every 6 hours
  - Oral prednisone: 40 mg/d

Antiviral Agents

- Acyclovir has reasonable activity against EBV in vitro.
  - Has not been shown to be beneficial in several clinical trials.
  - At this time, routine use is not recommended.
- Several antivirals (acyclovir, ganciclovir, vidarabine) and immunomodulating agents (interferon gamma, interferon alfa, interleukin 2) have been used in severe EBV infections.
  - Varying degrees of success
- Pharyngitis of infectious mononucleosis can be indistinguishable from that of streptococcal pharyngitis, and culture specimens of the pharynx should be obtained.
- Patients who have positive culture findings should be treated accordingly.
- Clinician should avoid using ampicillin or amoxicillin when EBV infection is suspected.
  - Rash develops in most young adults with EBV infection who receive this drug.
- Ampicillin effect has not been well demonstrated in young children with infectious mononucleosis.

Experimental Approaches

- For lymphoproliferative disease, a new reasonably successful approach is the use of anti-B-cell monoclonal antibodies (eg, anti-CD22).
- Approaches under investigation for the treatment of EBV-associated lymphoproliferative disease include
  - Bone marrow transplantation
  - Treatment with ex vivo expanded EBV-specific cytolytic T cells
  - Infusions of donor peripheral leukocytes

WHEN TO ADMIT

- Hospitalization may be necessary in the presence of
  - Airway compromise
  - Splenic rupture
  - Neurologic complications
  - Severe hemolytic anemia
  - Thrombocytopenia

WHEN TO REFER

- Consultation with appropriate subspecialists for the following complications would be warranted:
  - Airway compromise
  - Splenic rupture
  - Neurologic complications
  - Severe hemolytic anemia
  - Thrombocytopenia

FOLLOW-UP

- Many patients with chronic fatigue syndrome date the onset of their illness to an episode of infectious mononucleosis.
- Virologic and clinical studies have confirmed that active EBV infection is not responsible for the illness.
- At present, no single infectious or other cause has been identified for chronic fatigue syndrome.

COMPLICATIONS

- Death occurs in ~1 in 3,000 cases.
  - True complication and death rates during this illness are uncertain.
  - Many reports do not include strict diagnostic criteria for infectious mononucleosis.
- Relative frequencies (approximate) of more common complications associated with this illness from one study are
  - Pneumonia: 5%
  - Severe airway obstruction: 3.5%
  - Seizures: 4%
  - Meningitis, encephalitis: 2%
  - Peripheral facial nerve paralysis: 1%
  - Guillain-Barré syndrome: 1%
  - Thrombocytopenia with hemorrhages: 3.5%
  - Hemolytic anemia: 1%
  - Bacteremia: 1%
  - Recurrent tonsillopharyngitis: 3%
  - Jaundice: 2%
  - Glomerulonephritis: 1%
  - Orchitis: 1%

- Abdominal pain is an infrequent symptom of this illness.
  - Its appearance, particularly if severe and in the left upper quadrant, should alert the clinician to the possibility of impending or actual splenic rupture.
- Fatal cases of Reye syndrome associated with serologic evidence of EBV infection have been reported.
- EBV infection and cancer.
  - B lymphocytes that contain certain forms of EBV genome can divide indefinitely and potentially cause EBV-related cancers.
  - The virus remains latent in human hosts for the remainder of the host's life.
  - Some have speculated that EBV infection might be oncogenic in the United States.
  - Some cases of leukemia occurring shortly after the onset of infectious mononucleosis have been reported.
    - — No other evidence exists to support this speculation.
  - The association between EBV and classic Burkitt lymphoma is not as strong in the United States as in Africa.
  - The EBV genome can be detected in ~50% of Reed-Sternberg cells found in patients with the mixed cellularity form of Hodgkin lymphoma.
    - — Whether EBV is a causal agent, or even a cofactor, is unknown.
  - EBV is a known cause of nasopharyngeal cancers.
  - EBV has been associated with lymphoproliferative disease.
  - EBV has also been associated with several lymphoreticular cancers in patients with AIDS.
    - — Malignant B-cell lymphoma
    - — Colonic lymphoid hyperplasia
  - EBV has been associated with
    - — Oral hairy leukoplakia
    - — Lymphoid interstitial pneumonitis in individuals with AIDS
  - The precise relationship between EBV and cancer remains unknown and is the subject of intense investigation.

PREVENTION

- Secondary infection in typical college settings is low.
  - Strict isolation of the patient is unnecessary.
  - Separation of drinking and eating utensils (eg, avoiding drinking from the same glass) and avoidance of activities that cause saliva exchange are all that is required.

Munchausen Syndrome by Proxy: Medical Child Abuse

DEFINITION

- Medical child abuse (MCA), more widely known as Munchausen syndrome by proxy, is a rare form of abuse involving the persistent fabrication of physical or mental illness in a child by an adult.
  - Other names include pediatric condition falsification, factitious disorder by proxy, or fabricated or induced illness.
  - The fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (*DSM-5*) describes the syndrome as a "factitious disorder" with 2 types.
    - Factitious disorder imposed on self
    - Factitious disorder imposed on another
  - The American Professional Society on the Abuse of Children proposes
    - Pediatric condition falsification when focusing on the effect on the child
    - Factitious disorder by proxy when focusing on the perpetrator
- Occurs when
  - Child undergoes or receives unwarranted medical care.
  - Illness in a child is persistently and secretly simulated, produced, or both by a parent or someone in loco parentis.
    - Simulated: Caregiver perpetrator fabricates the child's symptoms.
    - Produced: Caregiver perpetrator secretly interferes with the child's body to produce symptoms or signs.
  - Often results in the parent(s) repeatedly bringing the child for medical care and, as a result, the child undergoes multiple unnecessary diagnostic and therapeutic medical procedures.
- Definition specifically excludes
  - Physical abuse only
  - Sexual abuse only
  - Failure to thrive that is solely the result of nutritional or emotional deprivation
- MCA poses different diagnostic and legal problems compared with other forms of child abuse.

SIGNS AND SYMPTOMS

- The most common serious presentation seems to be apnea.
- Seizures, feeding problems, bleeding, central nervous system depression, diarrhea, vomiting, fever (with or without sepsis or other localized infection), rash, allergy, and behavioral problems are also reported quite commonly (**Table 1**).

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Table 1. Some Clinical Presentations of Medical Child Abuse[a]

System	Symptom, Sign, Laboratory Finding, or Diagnosis
Head, eyes, ears, nose, throat, mouth	Bleeding from ears, nose, throat
	Conjunctivitis
	External otitis
	Hearing or speech impairment
	Nasal excoriation
	Nystagmus
	Otorrhea
	Parotitis or orbital cellulitis
	Tooth loss
Respiratory	Apnea or acute life-threatening event
	Asthma
	Bleeding from upper respiratory tract
	Choking or dyspnea

Table 1 (*continued*)

System	Symptom, Sign, Laboratory Finding, or Diagnosis
Respiratory (*continued*)	Cyanosis (and other color changes, including pallor)
	Cystic fibrosis
	Hemoptysis
	Respiratory arrest
	Respiratory infection
	Sleep apnea
Cardiovascular	Bradycardia
	Cardiomyopathy
	Cardiopulmonary arrest
	Hypertension
	Rhythm abnormalities (eg, bradycardia, tachycardia, ventricular tachycardia)
	Shock
Gastrointestinal	Abdominal pain
	Anorexia
	Bleeding from nasogastric tube or ileostomy
	Celiac disease
	Chronic intestinal pseudo-obstruction
	Crohn disease
	Diarrhea
	Esophageal burns
	Esophageal perforation
	Feculent vomiting
	Feeding problems
	Gastrointestinal ulceration
	Hematemesis
	Hematochezia or melena
	Hemorrhagic colitis
	Malabsorption syndromes
	Polyphagia
	Pseudomelanosis coli
	Retrograde intussusception
	Vomiting (cyclic or otherwise)
Genitourinary	Bacteriuria
	Hematuria
	Menorrhagia

Table 1 (*continued*)

System	Symptom, Sign, Laboratory Finding, or Diagnosis
Genitourinary (*continued*)	Nocturia
	Polydipsia
	Polyuria or impaired urinary concentrating ability
	Proteinuria
	Pyuria
	Renal failure
	Urethral stones
	Urine gravel
Neurologic, musculoskeletal, developmental, psychiatric	Arthralgia
	Arthritis
	Ataxia
	Behavioral or personality disorders (eg, anxiety, autism spectrum disorder, panic reactions, rage, disorientation)
	Cerebral palsy
	Developmental delay (failure to attain or loss of milestones, or both)
	Headache
	Hyperactivity
	Irritability
	Learning or attention-deficit disorder
	Lethargy
	Morning stiffness
	Psychotic symptoms
	Seizures
	Sleep disturbances: prolonged sleep, other sleep problems
	Syncope
	Tourette syndrome
	Unconsciousness
	Weakness
Skin	Abscesses
	Burns
	Eczema
	Excoriation
	Rash

Table 1 (*continued*)

System	Symptom, Sign, Laboratory Finding, or Diagnosis
Infectious, immune, allergic	Allergies (to food, drugs, or other substances)
	Bacteremia (unimicrobial or polymicrobial)
	Fevers
	Immunodeficiency
	Osteomyelitis
	Septic arthritis
	Sinopulmonary disease
	Soft-tissue or skin infection
	Urinary tract infection
Abnormalities of growth	Failure to gain weight or weight loss
Hematologic	Anemia
	Bleeding diathesis
	Bleeding from specific sites
	Easy bruising
	Leukopenia
Metabolic, endocrine, fluid, and electrolyte	Acidosis
	Alkalosis
	Creatine kinase and aldolase increase
	Cystinosis
	Dehydration
	Diabetes
	Electrolyte abnormalities
	Glycosuria
	Mitochondrial encephalopathy lactic acidosis and stroke-like syndrome
Other	Abuse (sexual, physical, or other)
	Diaphoresis
	Fatigue
	Foreign body ingestions
	Hypothermia
	Pain
	Peripheral edema
	Poisonings
	Preterm birth

[a] Including items reportedly observed by mother or actually observed by medical staff.

DIFFERENTIAL DIAGNOSIS

- An exhaustive differential diagnosis should be considered before concluding that MCA is the most likely answer.
  - Resist putting the child through painful and invasive testing if the likelihood of organic disease is small and MCA seems more likely.
- Factors that may be present in MCA include
  - Illness is multisystemic, prolonged, unusual, or rare.
  - Symptoms and laboratory results are incongruent with patient's presentation.
  - Symptoms disappear or diminish when caregiver is absent.
  - Caregiver has extensive medical knowledge or background.
  - Caregiver encourages medical staff to perform numerous tests and studies.
  - Caregiver is not reassured by patient progress or seemingly reassuring results.
  - Patient has multiple allergies to foods or medications.
  - Patient has poor response to standard therapies (eg, continued report of seizures at home after multiple anticonvulsants).
  - Patient unable to tolerate treatment (eg, frequent vomiting, rash, pain).
  - Often, caregiver's spouse is emotionally or physically absent or distant.
  - Family history may include complex medical diagnoses of parent or sibling or diagnoses that are difficult to confirm (eg, pregnancy complications, spontaneous abortion, sudden infant death syndrome [SIDS]).
  - Caregiver is sometimes admired for overwhelming devotion to patient's care or viewed as the model parent.
- If any of the following factors are present, MCA should be included in the differential diagnosis:
  - A history of repeated medical visits for unusual, poorly defined, unpredictable, or unresponsive illness, especially apnea and seizures
    - Symptoms never witnessed at their start by anyone other than a single caregiver.
    - Medical evaluation revealed no organic abnormality that might account for reported illness.
  - Ill sibling of decedent, especially with chronic, poorly defined medical problems
  - Dead sibling or unrelated child in the same home, especially if any of the following conditions are found:
    - Other child's death was signed out as SIDS.
    - Death followed a poorly defined or chronic illness.
    - Cause of death was allegedly an illness that overwhelmingly is nonfatal in childhood.
    - Cause of death was related to poisoning or intoxication.
    - Cause of death was the result of an unusual accident.
    - Death followed a presumed illness that was unsubstantiated or excluded at autopsy.
    - Explanation for the death was inadequate.
  - Mother with chronic, poorly defined medical problems
- Homicidal suffocation deaths are still too commonly misdiagnosed as SIDS.
  - If any significant history precedes death, SIDS is excluded by definition.
  - Concern is appropriate in sudden death of a child who had repeated apnea or acute life-threatening events before death, especially when attacks began only in the presence of a single caregiver.

DIAGNOSTIC APPROACH

- The single largest impediment to making a diagnosis is the failure to include MCA in the differential diagnosis.
- Early involvement of the MCA multidisciplinary team is critical for patient safety.
- The diagnostic strategy must maximize diagnostic capability while minimizing risk to the child.
- Strategies to confirm or eliminate diagnosis include
  - Review records.
  - Search for evidence of illness fabrication.
  - Search for evidence of an explanation other than MCA.
  - Separate the child from suspected perpetrator.
- Approach to records review when MCA is suspected.
  - Take note of inconsistencies between the caregiver's history and the observed clinical findings.
  - Compile a cumulative dated list of factors, eg, prescribed medications, operations, consultations, hospitalizations, diagnoses explored, diagnostic tests performed and their results, interventions attempted, and school days missed.

- Choose or design a test of the suspected fabrication (**Table 2**).
  - Set proper chain of evidence.
  - Preserve laboratory specimens.
  - Continuously monitor and record video units with plans to intervene immediately and decisively if assault is seen.
  - Establish precise coordination with law enforcement and social services.

LABORATORY FINDINGS

- Microbiology to determine whether the child was the victim of inflicted microbial assault
- Toxicology studies if poisoning is suspected
- Blood group typing, subtyping, or DNA typing if contamination with exogenous blood is suspected
- Routine toxicology in forensic examination following death

Table 2. Symptoms, Methods of Fabricating Illness, and Corresponding Diagnostic Strategies in Medical Child Abuse

Presentation	Method of Simulation, Production, or Both	Method of Diagnosis
Apnea	Manual suffocation	Video monitoring Implantable ECG recorder Diagnosis by exclusion Patient with pinch marks on nose Witnessed
	Poisoning: tricyclic antidepressants, hydrocarbons	Toxicology of gastric fluid, blood, urine, or IV fluid
Seizures	Fabrication	Diagnosis by exclusion
	Poisoning: phenothiazines, hydrocarbons, sulfonylurea, tricyclic antidepressants	Toxicology of gastric fluid, blood, urine, or IV fluid
	Salt	Serum and urine sodium concentrations
	Suffocation or carotid sinus pressure	Witnessed, forensic photographs of pressure points
Diarrhea	Phenolphthalein or other laxative poisoning	Stool or diaper positive
	Salt poisoning	Sodium concentrations of serum, urine or gastric contents; assay of formula
Vomiting	Emetic poisoning	Urine for drug
	Injection of air into gastrostomy tube	Video monitoring
	Fabrication	Hospital observation
CNS depression	Poisoning: diphenoxylate and atropine (Lomotil), insulin, clonidine, barbiturates or narcotics, benzodiazepines, aspirin, diphenhydramine, tricyclic antidepressants, acetaminophen, hydrocarbons, chlordiazepoxide, chloral hydrate, antiepileptics	Toxicology of blood, gastric contents, urine, IV fluid, hair; analysis of insulin type; video monitoring

Table 2 (*continued*)

Presentation	Method of Simulation, Production, or Both	Method of Diagnosis
Bleeding	Rodenticide (warfarin) poisoning	Toxicology
	Phenolphthalein poisoning	Diaper positive
	Exogenous blood applied	Blood group antigen profiling; DNA typing; ^{51}Cr labeling of erythrocytes
	Exsanguination of child	Witnessed
	Addition of substances (paint, cocoa, dyes)	Testing; washing
Rash	Drug poisoning	Assay
	Scratching	Diagnosis of exclusion
	Caustics applied/painting skin	Assay or wash off
	Contamination with infected material (saliva, feces, dirt)	Witnessed; type of organism growing from infected sites
Fever	Falsifying temperature	Careful charting, rechecking (especially rectal temperature or urine for core body temperature)
	Falsifying chart	Careful charting, duplication (ghost record) of temperature chart at nursing station

Abbreviations: CNS, central nervous system; ECG, electrocardiographic; IV, intravenous.

From Elsevier from Rosenberg DA. Web of deceit: a literature review of Munchausen syndrome by proxy. *Child Abuse Negl.* 1987;11(4): 547–563, with permission from Elsevier.

- Ask laboratory to preserve the samples securely because they may be needed for repeated studies or studies not originally considered.

IMAGING

- Skeletal survey to look for fractures

DIAGNOSTIC PROCEDURES

- Hidden video monitoring
  - Hospital security and the local police department should be aware of the video monitoring and available as needed.
  - Diagnostic, covert video monitoring in the hospital has engendered debate, with authors addressing legal, ethical, and logistic aspects.
  - Hospitals may collaborate with their legal team to develop a written policy; in some jurisdictions, a court order may be necessary.

CLASSIFICATION[1]

- Criteria for definitive diagnosis by inclusion
  - Child has been repeatedly presented for medical care *and*
  - Test or event is positive for tampering with child or with child's medical situation *and*
  - Positivity of test or event is not credibly the result of test error or misinterpretation or of miscommunication or specimen mishandling *and*
  - No explanation for the positive test or event other than illness falsification is medically possible *and*
  - No findings credibly exclude illness falsification.
- Criteria for a definitive diagnosis by exclusion
  - Child has been repeatedly presented for medical care *and*

- All diagnoses other than illness falsification have been credibly eliminated so that
  - If the child is alive, competing diagnoses are those that took into account the child's major medical findings and that account for the entirety of the child's presentation *or*
  - If the child is alive, separation of the child from the alleged perpetrator results in resolution of the child's reversible medical problems, in accordance with their degree and speed of reversibility. No variable other than the separation can logically and fully account for the child's improvement *or*
  - If the child is dead, autopsy examination does not reveal a cause of death that is credibly accidental, natural, or suicidal *and*
  - No findings credibly exclude illness falsification.

- Criteria for possible diagnosis
  - Child has been repeatedly presented for medical care *and*
  - Test or event result is presumptively positive for tampering with child or with child's medical situation. No other explanation is readily apparent. No findings seem to exclude illness falsification *or*
  - Child has a condition that cannot be fully explained medically, despite a respectable initial evaluation, at least. Cogent hypothesis suggests a faked medical condition. No findings seem to exclude illness falsification.
- Criteria for inconclusive determination
  - Child has been repeatedly presented for medical care *and*
  - The relevant and available information has been reviewed, the child has been appropriately evaluated, or both *and*
  - Physician is left with a differential diagnosis, rather than a single diagnosis *and*
  - Conclusively affirming one diagnosis is not possible *and*
  - It is not possible to conclusively exclude all but one diagnosis on the differential diagnosis.
- Criteria for excluding the diagnosis
  - Child has been repeatedly presented for medical care *and*
  - What had seemed to be possible falsification of illness has been wholly and credibly accounted for in some other way.

TREATMENT APPROACH

- Evaluation of the family is often stymied by the mother's refusal to participate or her indignant denial of her role in causing the child's illness.

SPECIFIC TREATMENTS

- The child should be protected while definitive data are collected to include or exclude the diagnosis.
- A multidisciplinary team should be involved early in the investigation.
  - Team should include the physician, bedside and supervising nurses, hospital social worker, and subspecialist physicians involved in patient's care.
  - County department of social services should be contacted.
  - Hospital attorney, hospital security, risk management, and hospital administrators and public relations personnel need to be involved.
  - Police and other law-enforcement personnel should be involved early.
    - If an episode of intentional infliction of harm comes to light during video monitoring, the police generally prefer to have prior knowledge of the case and may want to be prepared with an arrest warrant.
  - Psychiatrists or psychologists can evaluate the caregiver and evaluate the child from a developmental and psychological perspective and provide support after confrontation of the family with the suspected diagnosis.
- Medical records should be reviewed in a comprehensive and organized fashion.
  - Identify discrepancies between caregiver's history and documented laboratory and physical findings.
- All medical records of all siblings must be reviewed, including autopsy reports and death certificates.
- The parents' medical, educational, criminal, and work history should be reviewed, if possible.
- Several methods may be used, singly or in combination, to gain access to records.
  - Signed parental consent to obtain the records is possible.
  - Otherwise, attorneys may advise canvassing the area with subpoenas or requesting court-ordered record discovery.
- Presentation of the review of records to the multidisciplinary team should include a brief chronological review followed by a review of any discrepancies.
- Interview other family members about the child's illness and the mother's veracity.

- Recommending out-of-home placement for the child is prudent.
  - Simulators may become producers of illness.
  - Confrontation of the parent with the suspected diagnosis does not ensure safety for the child.
  - Placing the child with a family member or friend may be dangerous, as the perpetrator may have access to the child, despite promises to the contrary.
- A medically experienced person must supervise all hospital visits with family members to ensure that no one is tampering with the child's care.
  - This may mean asking the court for a short period of hospitalization with only supervised parental visits as a diagnostic trial.
  - This approach is useful if the child's symptoms and signs, if induced, would reasonably be expected to abate quickly in the absence of ongoing assault.
- Recommending out-of-home placement of siblings is prudent.
- Once the child is in foster care, health status must be monitored and documented closely by the same physicians.
- Deciding when to send the child home is difficult.
  - The guidelines that apply to other forms of child abuse and neglect should be applied in MCA.
  - Perpetrator must acknowledge these acts, must have some insight into the reasons for it, and must provide reasonable assurance that sufficient change has occurred to ensure the safety of the child.

WHEN TO REFER

- Anytime child abuse is suspected, a physician report to investigating agencies, including child protective services and law enforcement, is mandatory.
- When presenting a case to the civil or juvenile court, a short summary is often best.
- Physicians are not required to translate the degree of diagnostic conviction into a legal equivalent.
  - Medical language should be used and distilled into lay terms that best embody the physician's meaning.

FOLLOW-UP

- The mental health professional charged with providing initial assessment and ongoing therapy for the mother should have experience and expertise in MCA.
- The mother's therapist should discuss with the court and the child protection team specific issues that concern the safety of the child.
  - If the mother and the psychiatrist insist that all information is privileged, the court has no way to determine that the children will be safe at home and other permanent arrangements must be made.
- The health care system and physician may bear some responsibility for contributing to morbidity in MCA cases.

PROGNOSIS

- Very little information is available on family reunification after psychiatric intervention.
  - In one study, family reunification was thought to be feasible in certain cases, but the authors cautioned that long-term follow-up is necessary to monitor safety and assess whether the perpetrator's mental health has deteriorated.
- Even if children are removed permanently and parental rights are terminated, subsequent children born to the mother are at high risk.

PREVENTION

- Child fatality review teams are now common and are occasionally discovering cases of MCA that had been incorrectly designated as accidental, natural, or undetermined manners of death.

REFERENCE

1. From Rosenberg DA. Münchausen syndrome by proxy: medical diagnostic criteria. *Child Abuse Negl.* 2003;27(4): 421–430, with permission from Elsevier

DEFINITION

- Muscular dystrophies are a group of slowly progressive inherited diseases with specific patterns of muscle wasting and weakness.
- Duchenne muscular dystrophy is a slowly progressive muscle-wasting disease marked by symptoms that usually develop <5 years.
- Myotonic dystrophy type 1 is also called dystrophica myotonia (Steinert disease).
  - Myotonic dystrophy type 2 is distinct from but similar to myotonic dystrophy type 1 but does not occur in infancy or childhood.
- Facioscapulohumeral muscular dystrophy (FSHD) sometimes has onset in early childhood.
- Emery-Dreifuss muscular dystrophy (EDMD) is a rare, hereditary disorder with X-linked autosomal-dominant and autosomal-recessive forms that are clinically and genetically distinct from but occasionally confused with Becker muscular dystrophy.
- Limb-girdle muscular dystrophies (LGMDs) have a superficial resemblance to Duchenne muscular dystrophy.
  - Some can occur in childhood or in the late teens.

SIGNS AND SYMPTOMS

Duchenne Muscular Dystrophy

- Slowly progressive muscle-wasting disease marked by symptoms that develop <5 years.
  - Presents typically at 2–4 years of age
- Parents notice
  - Weakness of forward head flexion persisting beyond infancy
  - Slowed motor development
- Progressive gluteal and shoulder girdle muscular weakness leading to widened stance, lumbar lordosis, forward thrusting of abdomen, and toe walking.
- Patients never run normally and have difficulty keeping up with peers.
- Patients put hands on knees to rise from the floor (Gowers sign) and to assist in climbing steps.
- Early complaints (eg, toe walking, difficulty with stairs, language delay) are protean in nature.
- **Table 1** includes a detailed description of symptoms and tests for muscular dystrophies.

Other Childhood Muscular Dystrophies

- FSHD
  - Weakness of facial and bulbar muscles, generalized weakness, respiratory insufficiency.
  - FSHD type 1 and FSHD type 2 are indistinguishable clinically.
- EDMD
  - Produces severe cardiac complications requiring urgent treatment.
  - Cardiac complications may prompt medical evaluation before muscle weakness or contractures appear.
- LGMD
  - Most forms progress more slowly than Duchenne muscular dystrophy.
  - **Tables 2** and **3** outline the autosomal-dominant and autosomal-recessive forms of LGMD.

DIFFERENTIAL DIAGNOSIS

- A complete history almost always distinguishes Duchenne muscular dystrophy from other conditions that cause proximal weakness without sensory findings in childhood.
- DNA analyses and, only rarely, muscle biopsy are the appropriate diagnostic tests to establish the diagnosis of Duchenne muscular dystrophy.

Other Diseases With Similar Presentation to Muscular Dystrophies

- Intellectual disability
  - Mild cognitive deficits and language delay consideration of Duchenne muscular dystrophy or creatine kinase (CK) screening
- Cerebral palsy
  - Pattern of walking and presence of mild cognitive deficits can lead to an incorrect diagnosis of cerebral palsy.
  - Misdiagnosis delays effective treatment.
- Hypothyroidism, carnitine deficiency
  - Symptoms usually more generalized.
  - May be identified by blood tests.
  - Do not cause high CK levels that occur in Duchenne muscular dystrophy.
- Variants of spinal muscular atrophy, early onset LGMD
  - Hypertrophy of calf muscles.
  - Spinal muscular atrophy produces no increase or only mild increase in creatine phosphokinase.
  - Muscle biopsy distinguishes among forms of LGMD that are similar to Duchenne muscular dystrophy.
- Myasthenia gravis
  - More rapid development of weakness
  - Ptosis, ophthalmoplegia, and facial weakness
- Inflammatory myopathy
  - More rapid development of generalized weakness
  - Skin rash

(continued on page 743)

Table 1. Symptoms, Genetics, and Diagnostic Tests for Muscular Dystrophies in Childhood

Characteristics	Duchenne Muscular Dystrophy	Becker Muscular Dystrophy	Myotonic Dystrophy	Facioscapulohumeral Muscular Dystrophy	CMDs	EDMD
Age at onset	<5 y, typically at 2–4 y	>5 y; can begin in adult life	Infancy, childhood, or adult life	Rare cases in infancy; occasionally in childhood; usually in adult life	Infancy; <2 y	Middle to late childhood
Initial symptoms	Cannot run or keep up with peers; can take only one step at a time	Fatigue or marked thigh weakness; trouble climbing steps; occasional calf or thigh cramps; patients can ambulate beyond age 15 y.	Congenital form: floppy infant, poor suck, weak respiratory effort, talipes Childhood form: bifacial weakness, slurred speech, impaired hearing, intellectual disability	Congenital form (rare): bifacial weakness, sometimes ophthalmoplegia, occasionally floppy, deafness Childhood form (more common): mild facial weakness and weakness of scapular fixator muscles	Floppy infant; joint contractures, spinal rigidity, global developmental delay	Mild elbow contractures and mild weakness of triceps, biceps, and scapular fixator muscles; occasionally as isolated cardiomyopathy
Incidence	1:3,500 of male births	1:35,000 of male births	1:8,000 of all births	1:20,000 of all births	1:21,500 of all births	1:100,000 of all births
Genetics	X-linked recessive *XP21* region of gene for dystrophin	X-linked recessive *XP21* region of gene for dystrophin	Autosomal-dominant chromosome 19	Autosomal-dominant; most cases localize to chromosome 4	Autosomal-recessive except for 6-deficient CMD, which can be autosomal recessive or dominant, and *LMNA*-related CMD, which is inherited in an autosomal-dominant manner	X-linked recessive form Xq28 and autosomal-dominant form 1q21.3
Gene lesion	Mutation in the dystrophin gene	Marked deficiency of dystrophin	Abnormal expansion of CTG trinucleotide repeat in 3´ non-translated region of a gene coding for a serine/threonine kinase	Deletion of a variable quantity of 3.3-kb tandem repeats at 4q35 and abnormal methylation of the D4Z4 region	Defects of proteins in the basement membrane (laminin α_2 [ie, laminin α-2 deficient CMD]); defects of proteins in the extracellular matrix: collagen type VI–deficient CMD (Ullrich CMD); defects of glycosyltransferase enzymes resulting in abnormal glycosylation of α-dystroglycan (Walker-Warburg syndrome; Fukuyama type CMD); defects of proteins of the endoplasmic reticulum: selenoprotein	X-linked form involves gene for emerin and autosomal-dominant form gene for lamin A and C. Emerin and lamin A and C are attached to nuclear membrane. Their

Table 1 (*continued*)

Characteristics	Duchenne Muscular Dystrophy	Becker Muscular Dystrophy	Myotonic Dystrophy	Facioscapulohumeral Muscular Dystrophy	CMDs	EDMD
Gene lesion (*continued*)					N1 (rigid spine syndrome); defects of nuclear envelope proteins: lamin A and C and nesprin-1	functions are not yet known.
Serum creatine phosphokinase	10× above reference range	5–10× above reference range	Within reference range or 2–5× above reference range	2–5× above reference range	>10× above reference range	5–10× above reference range
Electrodiagnostic testing	Normal nerve conductions; myopathic EMG	Normal nerve conductions; mildly myopathic EMG	Normal nerve conductions; myotonic discharges present in children and adults but often absent in infants (EMG should be performed on the mother.)	Normal nerve conductions; EMG occasionally myopathic, often within reference limits	Normal nerve conductions; EMG myopathic	Normal nerve conductions; EMG often normal in early stages
Muscle biopsy	Active myopathy, absence of dystrophin, severe reduction in dystrophin-associated proteins	Moderately active myopathy, absence or deficiency of dystrophin, reduction in dystrophin- associated proteins	Increased central nuclei atrophy of type I fibers, ringbinden, and subsarcolemmal masses	Nonspecific myopathy; up to 30% have mononuclear inflammation.	Dystrophic changes with adipose and connective tissue replacement, and often prominent inflammatory infiltrates	Mild to moderate active myopathy with occasional atrophic type 1 fibers
Leukocyte DNA testing	If suspicion is high, perform DNA screening first. If leukocyte DNA test result is negative, perform muscle biopsy. DNA is screened for deletions and duplications (60%–70% have them); if deletion/ duplication is found, deletion tests are performed in at-risk	Same as Duchenne muscular dystrophy	If this diagnosis is suspected, a Southern blot analysis is performed to identify an abnormally large expansion of CTG repeats in the gene; if the Southern blot test result is typical, a polymerase chain reaction test is done to search for smaller expansion of the repeat; most childhood cases show abnormal CTG	DNA analysis available to identify the 3.3-kb deletions noted previously; should perform before obtaining muscle biopsy if clinical suspicion is high	*LAMA2; Col6A1-A2-A3; POMT1; POMT2; FKTN; FKRP; LARGE; POMGNT1; SEPN1; LMNA; SYNE1*	Mutations in the *EDMD* gene encoding emerin and *FHL1* gene encoding *FHL1* in X-linked *EDMD;* mutations in *LMNA* gene encoding lamin A and C for AD-EDMD and AR-EDMD

Table 1 (*continued*)

Characteristics	Duchenne Muscular Dystrophy	Becker Muscular Dystrophy	Myotonic Dystrophy	Facioscapulohumeral Muscular Dystrophy	CMDs	EDMD
Leukocyte DNA testing (*continued*)	family members; if no deletion is found, DNA sequencing for point mutation should be performed.		repeat enlargements (eg, 500–4,000 repeats), whereas normal alleles have 5–30 repeats.			

Abbreviations: AD-EDMD, autosomal-dominant Emery-Dreifuss muscular dystrophy; AR-EDMD, autosomal-recessive Emery-Dreifuss muscular dystrophy; CMD, congenital muscular dystrophy; CTG, cytosine-thymine-guanine; EDMD, Emery-Dreifuss muscular dystrophy; EMG, electromyography.

Table 2. Autosomal-Dominant Forms of Limb-Girdle Muscular Dystrophy

Disease Name	Gene	Chromosome Locus	Age of Onset	Creatine Kinase	Clinical Features	Other Features
LGMD-1A myotilinopathy	*MYOT* or *TTID*	5q31.2	≥18 y	Normal to moderately high	Proximal weakness; distal weakness late; ankle contractures	Dysarthria; dysphagia; respiratory insufficiency
LGMD-1B	*LMNA*	1q22	Birth to adulthood	Normal to high	Lower extremity weakness; late upper extremity weakness; contractures as in Emery-Dreifuss muscular dystrophy	Atrioventricular conduction defects; dilated cardiomyopathy
LGMD-1C caveolinopathy	*CAV3*	3p25.3	Any	Moderately to very high	Mild to moderate proximal weakness; cramps after exercise; myalgias	Calf hypertrophy; muscle rippling; hypertrophic cardiomyopathy
LGMD-1D desminopathy	*DES*	2q35	Early adulthood	Normal to moderately high	Mostly lower extremity weakness sparing quadriceps; ambulation preserved	Cardiac conduction defects; dilated cardiomyopathy
LGMD-1E	*DNAJB6*	7q36.3	18–40 y; late onset in females	Normal to moderately high	Slowly progressive weakness in lower extremities sparing quadriceps	Calf hypertrophy; loss of ambulation 20–30 y from onset
LGMD-1F	*TNP03*	7q32.1-q32.2	Any	Normal to high	Fast progression in early onset cases; facial weakness	Scoliosis; respiratory failure
LGMD-1G	*HNRPDL*	4q21	Adulthood	Normal to very high	Proximal lower extremity weakness	Finger and toe flexion limitation
LGMD-1H	Not known	3p25-p23	Second to fifth decade	Normal to very high	Slowly progressive upper and lower extremity weakness	Calf hypertrophy; muscle atrophy; high serum lactate

Abbreviation: LGMD, limb-girdle muscular dystrophy.

Table 3. Autosomal-Recessive Forms of Limb-Girdle Muscular Dystrophy

Disease Name	Gene and Chromosome Locus	Age at Onset	Creatine Kinase	Clinical Features	Other Features	Other Phenotypes
LGMD-2A calpainopathy	*CAPN3;* 15q15	8–15 y; rarely late	High to very high	Mild to severe weakness; difficulty running; calf atrophy	Toe walking; early ankle contractures; scoliosis	NA
LGMD-2B dysferlinopathy	*DYSF;* 2p13.2	15–25 y	High to very high	Weakness and atrophy of pelvic >shoulder girdle muscles; difficulty running; late upper extremities involvement	Calf and biceps atrophy; deltoid "bulge"; mean age at loss of ambulation: 45 y	Miyoshi myopathy; distal myopathy with anterior tibial involvement
LGMD-2C, -2D, -2E, -2F SGs	2C: *SGCG;* 13q12 2D: *SGCA;* 17q21.33 2E: *SGCB;* 4q12 2F: *SGCD;* 5q33	Childhood	High to very high	Severe progression "Duchenne-like"; milder course also possible	Calf hypertrophy	Dilated cardiomyopathy (δ-SG)
LGMD-2G	*TCAP;* 17q12	2–15 y	Moderately high	Proximal and distal weakness; difficulty running	Calf hypertrophy; footdrop	Dilated cardiomyopathy
LGMD-2H	*TRIM32;* 9q33.1	First to second decade	Normal to very high	Weakness; flat smile	Wasting	Myopathy
LGMD-2I	*FKRP;* 19q13.3	Prenatal	High to very high	Severe; progressive	Calf and tongue hypertrophy; pectoralis atrophy	Severe CMD
LGMD-2J	*TTN;* 2q24.3	2–25 y	High to very high	Severe; progressive proximal weakness	Distal weakness late in 50% of cases	Distal myopathy; dilated cardiomyopathy
LGMD-2K	*POMT1;* 9q34.13	Prenatal First decade	Very high	Mild proximal weakness	Microcephaly; low IQ	Walker-Warburg syndrome
LGMD-2L	*ANO5;* 11p14.3	Adulthood	Very high	Pelvic girdle weakness or calf hypertrophy; difficulty walking on tiptoe	Asymmetric quadriceps and biceps atrophy	Occasional Miyoshi-like myopathy
LGMD-2M	*FKTN;* 9q31	Prenatal	Very high	Rigid spine; viral-induced worsening weakness	Facial and axial weakness	Fukuyama type CMD

Table 3 (*continued*)

Disease Name	Gene and Chromosome Locus	Age at Onset	Creatine Kinase	Clinical Features	Other Features	Other Phenotypes
LGMD-2N	*POMT2;* 14q24	Prenatal First decade	Very high	Scapular winging; slow running; motor delay	Calf hypertrophy	Walker-Warburg syndrome
LGMD-2O	*POMGnT1;* 1p34.1	Prenatal First decade	High	Mild to moderate weakness	Myopia	Muscle-eye-brain type of CMD
LGMD-2P	*DAG1;* 3p21	Prenatal Early first decade	Very high	Mild weakness; muscle hypertrophy	Microcephaly; intellectual deficiency; normal brain imaging	NA
LGMD-2Q	*PLEC1;* 8q24	Prenatal Early first decade	Very high	Progressive proximal weakness; ptosis; dysphagia; facial weakness	Scapular winging; absent deep tendon reflexes	Epidermolysis bullosa simplex with muscular dystrophy; as previously described with myasthenia
LGMD-2R	*DES;* 2q35	Second and third decade	Mildly elevated	Progressive proximal weakness	Atrioventricular cardiac conduction defects; no cardiomyopathy	NA
LGMD-2S	*TRAPPC11;* 4q35	First decade	High	Slow to moderate progressive weakness	Ataxia; intellectual deficiency; hyperkinetic movements	NA
LGMD-2T	*GMPPB;* 3p21	First and second decades	High	Occasional proximal weakness pattern	Microcephaly; intellectual delay	NA
LGMD-2U	*ISPD;* 7p21	Prenatal First, second, or third decade	High to very high	Progressive weakness (similar to Duchenne muscular dystrophy); calf and tongue hypertrophy	Respiratory insufficiency; cardiac dysfunction	Walker-Warburg syndrome; cobblestone lissencephaly
LGMD-2V	*GAA;* 17q25.3	Wide range, infancy to seventh decade	Moderate to high	Progressive muscle weakness	Respiratory insufficiency	Pompe disease in early childhood

Abbreviations: CMD, congenital muscular dystrophy; LGMD, limb-girdle muscular dystrophy; NA, not applicable; SG, sarcoglycanopathy.

- Chronic demyelinating polyneuropathy
  - Absence of ankle reflexes
  - More generalized weakness
  - More rapid course
  - No marked increase of CK levels
  - Abnormally slowed nerve conduction
- Pompe disease
  - Glycogen storage disease type II.
  - Presenting symptoms include progressive weakness and hypotonia.
  - Cardiomegaly and hepatomegaly are common.
  - CK level is elevated.
- Floppy infants
  - Can have markedly increased serum CK levels in rare cases.
    - — Newborns or infants with Duchenne muscular dystrophy also have a marked increase in CK levels, but they are not floppy.
  - The floppy infant without an infectious, toxic, or metabolic disorder that causes muscle destruction to account for marked increase of serum CK level.
    - — Usually has 1 of 2 relatively rare muscular dystrophies noted in **Tables 1** and **4.**
  - Certain congenital myopathies may be marked by floppiness.
    - — These infants do not have significantly increased CK levels.

DIAGNOSTIC APPROACH

- Complete history.
  - Almost always distinguishes muscular dystrophy from other conditions that cause proximal weakness without sensory findings in childhood
- In suspected cases, serum CK levels should be measured first.
  - A marked increase is suggestive of a muscular dystrophy.
    - — Detailed discussion of natural history of Duchenne muscular dystrophy or procedures for screening at-risk family members for carrier status is premature and best initiated after neurologic consultation and specific diagnostic data are available.
- The clinician should refer the patient for further evaluation to a neurologist skilled in the care of patients with neuromuscular disease.

LABORATORY FINDINGS

- Once diagnosis of Duchenne or Becker muscular dystrophy is suspected, serum CK levels should be measured promptly.
- Myotonic dystrophy type 1.
  - Genetic tests to identify symptomatic and asymptomatic carriers.
  - Genetic counseling and prenatal testing have a high degree of accuracy.
- A continuously updated list of laboratories and tests available for the genetic diagnosis of Duchenne muscular dystrophy can be found at GeneTests.

DIAGNOSTIC PROCEDURES

- See **Table 1.**

TREATMENT APPROACH

Duchenne Muscular Dystrophy

- Goals.
  - Maintain ambulation for as long as possible.
  - Optimize development of the patient's cognitive abilities.
  - Anticipate complications.
- **Table 4** summarizes principle problems and treatment options.
- Develop an individualized care plan for each stage of disease.
  - Patient and family working closely with physicians, schoolteachers, physical educators, and physical and occupational therapists
- Muscular Dystrophy Association clinics offer multiple services to patients.
- Orthopedic care, physical therapy, occupational therapy, and neurologic care are coordinated by a neuromuscular specialist.
  - Typically, services are provided in a clinic financed partly by the Muscular Dystrophy Association.
  - Role of primary care physician remains critical.
    - — The pediatrician usually provides routine care of upper respiratory infections, routine immunizations, and treatment for other common medical problems.

SPECIFIC TREATMENTS

Supportive Care

- Orthopedic management, physical therapy, occupational therapy, and neurologic care coordinated by neuromuscular specialist, often in a specialized clinic.
- Physical therapy often consulted at diagnosis or 4–6 years of age.
  - Emphasis on range of motion and home stretching, especially for ankles.

Table 4. Complications and Treatment of Muscular Dystrophies in Childhood

Characteristics	Duchenne Muscular Dystrophy	Becker Muscular Dystrophy	Myotonic Dystrophy	Facioscapulohumeral Muscular Dystrophy	Congenital Muscular Dystrophies	Emery-Dreifuss Muscular Dystrophy
Muscle weakness	Treatment with prednisone or deflazacort slows deterioration or stabilizes muscle strength.	No controlled studies of prednisone treatment	No specific therapy; braces for footdrop; children can usually participate in physical education in school.	No specific treatment; patients should avoid lifting with arms fully extended and abducted; braces are sometimes needed.	No specific treatment; bracing and physical therapy are useful in some patients.	No specific treatment; skeletal muscle weakness is often relatively mild compared with cardiac problems and does not limit function.
Respiratory problems	Forced vital capacity is monitored (in later stages, atelectatic pneumonitis is common); colds are treated aggressively; if signs of respiratory failure develop, nasal or oral ventilation should be considered.	Uncommon until late stages; management then as with Duchenne muscular dystrophy	For congenital cases, ventilation is often needed; prognosis for survival is poor if the patient is ventilator dependent at >4 wk; other management is as for Duchenne muscular dystrophy.	Uncommon	As with Duchenne muscular dystrophy; patients often die of respiratory failure late in childhood or in early teens.	Mild other than symptoms related to cardiac dysfunction
Cardiac problems	Cardiomyopathy often leads to congestive heart failure in late stages of the disease; afterload-reducing therapy often helps; patient should be monitored for intracardiac clots.	Severe cardiomyopathy may require cardiac transplant; congestive heart failure treatment is the same as for Duchenne muscular dystrophy.	Occasionally, tachyarrhythmia or heart block develops in childhood, and pacemaker treatment is indicated.	Uncommon	Uncommon	Frequent cardiac conduction defects, atrial paralysis, cardiac arrest, and sudden death are common; pacemaker treatment and preventive therapy for cardiac emboli are often necessary.

Table 4 (*continued*)

Characteristics	Duchenne Muscular Dystrophy	Becker Muscular Dystrophy	Myotonic Dystrophy	Facioscapulohumeral Muscular Dystrophy	Congenital Muscular Dystrophies	Emery-Dreifuss Muscular Dystrophy
Orthopedic problems	Achilles tendon contractures respond to stretching in early stages; later, tendon release surgery is sometimes performed; contractures at the hips, knees, elbows, and wrists usually develop after the patient becomes wheelchair limited; scoliosis often develops when patients stop ambulating; spinal stabilization surgery is often unnecessary in patients receiving long-term corticosteroid treatment. Risk vs benefit depends on total medical picture, and some patients may experience a slowing in rate of weakness in pulmonary function. Role of spinal stabilization surgery is currently being reevaluated.	Uncommon; contractures are much less common than in Duchenne muscular dystrophy.	Talipes deformity requires treatment with stretching and orthotic support; occasionally, surgery is necessary.	Occasionally, knee effusion and low back pain develop as a result of weakness; conservative care measures are effective; in late stages, surgery to stabilize the scapula may be performed, but surgery is uncommon.	Contractures develop in 70% of patients by 3 mo at the ankles, knees, hips, and feet.	Contractures, especially in the elbows and ankles, occur early and respond somewhat to physical therapy; surgical release of Achilles tendon may be necessary; some patients develop a rigid spine syndrome, for which no effective therapy is available.
Nervous system problems	Increased incidence of cognitive and behavioral problems; some patients improve with small doses of methylphenidate.	Uncommon	Intellectual disability is common, especially in congenital cases, and special classroom care is needed; hearing deficits are common and may require hearing aids; facial weakness, dysarthria, and hearing problems exaggerate the impression of intellectual disability.	Uncommon; in rare cases, the infant-onset form of the disease occurs in association with hearing loss, retinal disease, or both.	Severe intellectual disability is common; magnetic resonance imaging of head shows increased signal from white matter on T2-weighted images; occipital agyria; most patients have microcephaly, polymicrogyria, pachygyria, and heterotopias; generalized or focal seizures occur in most patients; anticonvulsant therapy is necessary.	Caused only by stroke from heart block or cardiac emboli

Table 4 (*continued*)

Characteristics	Duchenne Muscular Dystrophy	Becker Muscular Dystrophy	Myotonic Dystrophy	Facioscapulohumeral Muscular Dystrophy	Congenital Muscular Dystrophies	Emery-Dreifuss Muscular Dystrophy
Gastrointestinal problems	Constipation is common, especially late in the disease; careful dietary monitoring, stool softeners, and good water intake (urine specific gravities 1.007–1.010) are usually effective; occasionally, acute gastric dilation occurs; it resolves over 2–3 d with nasogastric tube decompression of the stomach and intravenous hydration.	Uncommon	Spastic colon–type complaints with abdominal pain are common; occasionally, these symptoms improve with anti-myotonia therapy with mexiletine; eating small portions at each meal diminishes tendency to aspirate.	Uncommon	Uncommon	Uncommon

- Contractures and scoliosis develop when child is no longer able to ambulate.
- Avoid strengthening programs; reserve energy for fun and functional activities.
- Aquatherapy if available.
- Need for tendon release surgery and spinal stabilization surgery for scoliosis has declined since steroid use became standard of care.
  - Spinal stabilization surgery decision should be coordinated with consultants in orthopedics, pulmonary medicine, cardiology, and neuromuscular.
- Primary care physician usually provides routine care of common medical problems.
  - In middle to late nonambulatory stages of Duchenne muscular dystrophy, minor medical problems can lead to major complications.
  - Pulmonary function monitoring in consultation with pulmonary medicine specialists
    - Nocturnal hypoventilation
    - Noninvasive support with continuous positive airway pressure (CPAP) or biphasic positive airway pressure (BiPAP)
- Cardiomyopathy often seen in late stages of Duchenne muscular dystrophy.
  - Dilated heart on chest radiograph
  - Ejection fraction decreased to 10%–20% of reference range
- Heart failure.
  - Exacerbated by respiratory insufficiency
  - Managed initially by trial with angiotensin-converting enzyme inhibitor (eg, lisinopril)
  - If left-ventricular function worsens, treatment with β-blocker therapy (eg, carvedilol) to keep heart rate at 55–70 beats per minute
- If present, ventricular and atrial clots managed with long-term anticoagulant therapy.
- Gastric dilation is infrequently seen in late stages of Duchenne muscular dystrophy, typically in association with idiopathic metabolic acidosis.
  - Nasogastric tube decompression and intravenous hydration.
  - Caution must be used in repletion of potassium because of diminished muscle mass in late stages of the disease.
  - Prevention of this and constipation with
    - Hydration, balanced diet, regular bowel habits

Corticosteroid Therapy

- Corticosteroids (prednisone and deflazacort) are the only effective, evidence-based therapy for Duchenne muscular dystrophy.

- Treatment, though routine, is not approved by the US Food and Drug Administration in the United States, but it is used in Canada and Europe.
  - — Best carried out in medical centers experienced with Duchenne muscular dystrophy
- Short- and long-term treatment to maintain muscle strength and function.
- Increased strength begins after 10 days of treatment and reaches maximal response after 3 months of therapy.
- Muscle mass increases 10% after 3 months on prednisone.
- Rate of muscle breakdown declines with maintenance of normal rate of muscle protein synthesis.
- Long-term benefits include prolonged ambulation and stabilization of pulmonary function, reduced need for spinal stabilization surgery, and improved quality of life.
- Side effects include
  - — Short stature.
  - — Weight gain.
  - — Mood disturbances.
  - — Cushingoid facial appearance.
  - — Serious side effects are uncommon (eg, compression fractures, delayed puberty, hypertension, gastrointestinal bleeding, infections, diabetes).
- In late stages, prednisone seems to maintain respiratory muscle power and has reduced the number of patients who develop respiratory failure.

- Steroids have no direct effect on contracture formation except secondary to maintaining proximal muscle strength.
- Azathioprine immunosuppressive therapy confers no beneficial effect.
- Research for future treatments.
  - Genetic discoveries and the ability to manufacture segments of DNA with a normal gene for dystrophin has raised hope for direct gene therapy.
  - Cost-effective newborn screening with CK is being studied to identify patients for novel therapeutic approaches prior to clinical symptoms.

WHEN TO ADMIT

- After surgery
  - For 24 hours (or longer, depending on type of surgery) to monitor cardiac and pulmonary function
- For evaluation and management of pneumonia or respiratory insufficiency, especially in
  - Nonambulatory patients with Duchenne muscular dystrophy
  - Patients with advanced cardiomyopathy with cardiac failure

WHEN TO REFER

- Neuromuscular clinic or specialist
  - When diagnosis of Duchenne muscular dystrophy is strongly suspected (ie, symptoms and high CK levels)
  - To facilitate workup
  - Once diagnosis is confirmed to establish multidisciplinary care
- Genetic counselor
  - After the diagnosis of Duchenne muscular dystrophy is established
  - Offered to family members of patients, especially women at risk for mutations based on family history or symptoms
- Cardiologist
  - At diagnosis to obtain baseline cardiologic evaluation
  - If any wall motion abnormality is present on echocardiogram, delayed enhancement on cardiac magnetic resonance imaging, or suspicion of arrhythmia
  - In the late stages of the disease for monitoring of cardiac function and management of cardiomyopathy and heart failure
  - Before surgery
- Pulmonologist
  - To obtain a baseline pulmonary evaluation at time of diagnosis
  - In late nonambulatory stage of disease to monitor forced vital capacity, cough pick flow, maximum inspiratory pressure, and maximum expiratory pressure and manage respiratory failure with noninvasive ventilatory support
  - To discuss tracheostomy
  - Before surgery to maximize use of cough assist and BiPAP as necessary
- Orthopedic surgeon
  - To obtain a baseline orthopedic consultation at time of diagnosis
  - After the patient with Duchenne muscular dystrophy has lost ability to walk
  - For consideration of scoliosis surgery or release of heel cord contractures when the nonambulatory patient shows signs of spinal curvature or progressive heel cord contractures

- Physical and/or occupational therapist
  - During the ambulatory stage of Duchenne muscular dystrophy to develop a heel cord stretching program and an individualized exercise program
  - In the late ambulatory stage of Duchenne muscular dystrophy when the patient may seem to be close to becoming wheelchair limited
  - To be fitted with adaptive equipment and night braces
  - To evaluate and manage contractures
- Dietitian
  - During ambulatory stage of Duchenne muscular dystrophy, particularly in patients receiving corticosteroid treatment
  - To help manage weight gain
  - To establish healthy eating patterns for the future
- Neuropsychologist
  - During ambulatory and nonambulatory stages of Duchenne muscular dystrophy because patients are at risk for emotional, cognitive, and behavioral problems
  - For patients
    - With borderline intellectual abilities
    - With cognitive or behavioral abnormalities
  - For patients and family members who need end-of-life counseling

FOLLOW-UP

- Monitoring for side effects of prednisone
  - Patients are seen every 3–6 months for
    - Weight check
    - Blood pressure check
    - Pulse check
    - Forced vital capacity check
    - Urinalysis
    - Neuromuscular functioning assessment
  - Each visit includes measures to help guide the physician in adjusting the dose of prednisone.
    - Timed function tests
      - Time needed to travel 30 feet, to arise from supine to standing position, and to climb 4 standard steps
    - Muscle strength evaluation
      - Shoulder abductors
      - Elbow flexors and extensors
      - Knee extensors
      - Hip flexors and extensors
  - Blood cell count and serum electrolyte levels are measured at 6-month intervals.
- Routine care of upper respiratory infections, immunizations, and common medical problems

COMPLICATIONS

- **Table 4** summarizes principal complications and treatment options of childhood muscular dystrophies.
- Minor medical problems can provoke major complications.
  - Mild cold may lead to atelectatic pneumonitis and acute respiratory insufficiency.
  - Chronic constipation can produce respiratory compromise from upward pressure by distended abdomen.
- Respiratory insufficiency.
  - Often develops in late stages of Duchenne muscular dystrophy
    - Forced vital capacity declines to a range of 600–1,000 mL.
    - Manage with nasal ventilation rather than positive pressure ventilation via tracheostomy in most patients.
    - Monitor pulmonary function and screen for nocturnal hypoventilation and obstructive sleep apnea.
    - Coordinate care with pulmonary consultants.
    - Initiate noninvasive nighttime respiratory support with CPAP or BiPAP.

PROGNOSIS

- With steroid therapy and close follow-up, patients have remained stable or with only mild progression of muscle weakness for >5 years.
- Natural history of Duchenne muscular dystrophy without corticosteroid treatment.
  - Wheelchair predicted for independent mobility between 10 and 12 years of age

DEFINITION

- *Nephritis* refers to noninfectious inflammation of the kidney parenchyma, which may involve primarily the glomerulus (glomerulonephritis), the tubules and interstitium (tubulointerstitial nephritis), or both.
- Acute glomerulonephritis.
  - Most commonly, acute poststreptococcal glomerulonephritis (APSGN)
  - Henoch-Schönlein purpura (HSP) is small-vessel vasculitis that most often affects children.
  - Rapidly progressive glomerulonephritis (RPGN) is a variant of acute glomerulonephritis characterized by
    - Symptoms of acute nephritis
    - Relentless progression to renal failure over weeks or months
- Chronic glomerulonephritis is associated with a variety of conditions.
  - Immunoglobulin A (IgA) nephropathy (Berger disease)
  - Benign familial hematuria
  - Alport syndrome
  - Nephritis of systemic lupus erythematosus (SLE)
  - Membranoproliferative glomerulonephritis (MPGN)
    - Group of chronic inflammatory diseases of the kidney with poor prognosis
    - Idiopathic (immune complex-mediated diseases; formerly MPGN types 1 and 3, with immunoglobulin present by immunofluorescence microscopy [IFM])
    - Third component of complement (C3) glomerulopathies, which include dense deposit disease (DDD; formerly MPGN type 2) and C3 glomerulonephritis (C3GN; formerly MPGN types 1 and 3, but lacking immunoglobulin staining by IFM)
  - Interstitial nephritis
    - Inflammation of the tubules and interstitium of the kidney
    - Underappreciated cause of acute kidney injury

SIGNS AND SYMPTOMS

General

- Periorbital or pretibial edema
- Changes in eye grounds
- Uremic odor to the breath
- Pleural or pericardial friction rubs
- Ascites
- Costovertebral angle tenderness
- Joint swelling or tenderness
- Vasculitic rashes
- Hematuria, microscopic or macroscopic
- Proteinuria
  - Proteinuria can range from mild to nephrotic.
  - The finding of hematuria and proteinuria together strongly suggests underlying glomerular inflammation.
- Erythrocyte casts in the urine

Acute Glomerulonephritis

- Abrupt onset of
  - Hematuria
    - Often grossly visible as tea-colored or cola-colored urine
    - May be microscopic only
    - Erythrocyte casts and dysmorphic erythrocytes, although several urine samples may have to be examined
  - Proteinuria
  - Hypertension
  - Edema
- APSGN
  - Characteristically occurs
    - 1–4 weeks after infection caused by nephritogenic streptococci
    - Slightly longer lag time after a pyoderma
  - Most patients exhibit macroscopic hematuria.
  - Usually oliguria.
  - Rarely anuria.
  - Edema that is usually periorbital and, rarely, severe.
  - Signs of congestive heart failure.
  - Hypertension.
    - If severe, may produce headache, drowsiness, vomiting, personality and visual changes, and convulsions
  - Anorexia.
  - Pain in the abdomen or flank are common, although palpation of the abdomen usually does not reveal significant findings.
  - Costovertebral angle tenderness.

HSP Nephritis

- Palpable purpuric lesions.
- Arthritis.
- Abdominal pain.
- Gastrointestinal bleeding.
- Not all manifestations need be present at the same time.

IgA Nephropathy

- Characteristically, sudden onset of painless gross hematuria concomitant with an infection, usually of the respiratory tract.
  - May be associated with flank pain.
  - Usually clears within a few days to a week as the infection resolves.
  - Frequently recurs with subsequent infections.
  - Microscopic hematuria may persist with or without proteinuria between episodes.
    - More common presentation in Asia
  - Urine may clear totally.
- ~10% may have nephrotic syndrome or acute kidney injury at presentation.

Benign Familial Hematuria

- Persistent asymptomatic microscopic hematuria in the absence of
  - Hearing loss
  - Proteinuria
  - Progressive renal impairment

Alport Syndrome

- Persistent microscopic hematuria is found early in all affected male patients.
- Most female patients have intermittent microscopic hematuria.
- Macroscopic hematuria is often seen at time of respiratory infection.
  - In ≤70% of male patients
  - In 33% of female patients
- Proteinuria in males; nephrotic range in ~30%.
- Sensorineural hearing loss.
  - Not present at birth
  - Progressive starting with high frequencies
  - Affects male patients more than female patients
- Eye abnormalities in ~50% of patients.
  - Anterior lenticonus
  - Retinal abnormalities
  - Corneal ulcerations
- Two-thirds of patients with the autosomal-recessive form develop hearing loss.
- Half the carriers of the abnormal gene also have microscopic hematuria.

SLE Nephritis

- Initial symptoms may be vague; a high index of suspicion is warranted.
  - Childhood SLE tends to be more severe at presentation than adult-onset SLE.
  - SLE may cause acute glomerulonephritis.
- Initially may have constitutional, cutaneous, or musculoskeletal symptoms, such as
  - Fever
  - Neuropsychiatric manifestations
    - Malaise
    - Emotional liability
  - Malar erythema
  - Photosensitivity
  - Raynaud symptoms
  - Myositis
  - Multiple joint arthritis
  - Pericarditis
  - Pleuritis
- Renal involvement in ≤75% of cases, characterized by
  - Isolated hematuria
  - Hematuria with proteinuria
  - Nephrotic syndrome
  - Hypertension
  - Rapidly progressive renal failure

MPGN

- Average age of onset of primary MPGN in children is 10 years.
- Children with MPGN can present with
  - Asymptomatic hematuria and proteinuria
  - Gross hematuria
  - Nephritis
  - Nephrotic syndrome
  - Hypertension
  - Decreased renal function
- Presentation may vary according to histologic subtype.
- Patients with acquired partial lipodystrophy often have circulating nephritic factors and low C3 blood levels.
- 20% develop DDD.

Interstitial Nephritis

- Unexplained acute kidney injury.
- Proteinuria.
- Leukocyturia.
- Microscopic hematuria.
- Fever and eosinophilia in one-third of patients.
- Rash in 20% of patients.
- Uveitis may precede, occur spontaneously with, or follow onset of renal disease.

DIFFERENTIAL DIAGNOSIS

- Clinical syndrome can have 2 presentations: acute glomerulonephritis with no or mild renal failure and acute glomerulonephritis with rapidly progressive renal failure.

- Non-streptococcal glomerulonephritis.
  - Some infectious agents, such as *Staphylococcus aureus, Mycoplasma* species, and gram-negative bacilli, can be associated with crescent formation and rapid deterioration of renal function.
- Glomerulonephritides with low complement levels.
  - APSGN
    - Evidence of a preceding streptococcal infection can be important to support the diagnosis.
    - Failure of complement levels to normalize by 6–8 weeks suggests another form of nephritis, such as MPGN, nephritis of chronic infection, or SLE nephritis.
  - SLE nephritis
  - MPGN
  - Nephritis of chronic infection
  - Cryoglobulinemia
- RPGN with immune complex.[1]
  - Postinfectious reaction
    - Streptococcal infection
    - Visceral abscess
    - Other
  - Collagen-vascular disease
    - SLE
    - HSP
    - Mixed cryoglobulinemia
  - Primary renal disease
    - IgA nephropathy
    - MPGN
    - Unknown cases (ie, idiopathic)
- RPGN with no immune deposit.[1]
  - Unknown cause
  - Vasculitis
    - Microscopic polyangiitis
    - Wegener granulomatosis with upper and lower respiratory findings
    - Hypersensitivity vasculitides
    - Churg-Strauss syndrome with extravascular granulomas
    - Hypereosinophilia
    - Asthma
    - Atopic allergies
  - Hemolytic uremic syndrome
- RPGN with anti–glomerular basement membrane (GBM) antibody.[1]
  - With lung hemorrhage (Goodpasture syndrome)
  - Without lung hemorrhage
  - Complicating membranous nephropathy
- Acute glomerulonephritides characterized by no or mild renal failure.
  - More common
    - APSGN
    - HSP with nephritis
      - IgA nephropathy is difficult to differentiate morphologically from HSP.
      - Has led to speculation that HSP is a form of IgA nephropathy with systemic findings.
    - Postinfectious (non-streptococcal) glomerulonephritis
    - Interstitial glomerulonephritis
    - Radiation nephritis
  - Less common
    - Acute episodes in patients with chronic glomerulonephritis
    - Hemolytic uremic syndrome (milder cases)
    - MPGN (some)
    - SLE nephritis (some)
- Only a family history of lack of progressive renal impairment, deafness, and eye findings distinguishes benign familial hematuria from early Alport syndrome.
- IgA nephropathy.
  - Simultaneous onset of upper respiratory tract infection with gross hematuria helps differentiate this from APSGN, in which delay between infection and hematuria is the rule.
  - Absence of a rash, abdominal pain, and arthritis helps differentiate from HSP nephritis.

DIAGNOSTIC APPROACH

- If nephritis is suspected
  - Blood pressure should be monitored carefully and frequently and compared with normal values for sex, age, and height percentile.
  - Weight should be measured.
    - Significant weight gain might suggest fluid retention.
  - Poor growth with crossing height percentiles with inappropriate weight gain or loss might suggest a chronic renal disorder.
- Follow up with appropriate laboratory, imaging, and biopsy studies.

LABORATORY FINDINGS

General

- Initial laboratory evaluation should include
  - Urinalysis with microscopy
  - Serum electrolytes
  - Blood urea nitrogen

- Creatinine
- Calcium
- Phosphorus
- Albumin
- Liver enzymes
- Complete blood cell count with platelets
- Complement levels
  - — Decreased levels of C3 and, on occasion, fourth component (C4), can help narrow the differential diagnosis by distinguishing the hypocomplementemic nephritides from those with normal complement levels.
- Antinuclear antibody and antistreptolysin O or other antibodies to streptococcal antigens

- Lupus nephritis, Wegener granulomatosis, microscopic polyangiitis, and some cases of MPGN or membranous nephropathy
  - Anti–double-stranded DNA
  - Antineutrophil cytoplasmic antibodies
  - Hepatitis B and C serologic tests
- Unclear cases
  - Urine culture

Acute Glomerulonephritis

- Leukocytes on microscopy and positive test result for leukocyte esterase are often found and suggest inflammation rather than bacterial infection.
- Red blood cell casts and dysmorphic red blood cells are present, although several urine samples may have to be examined.

APSGN

- Urine is usually tea colored and opaque.
- Urine specific gravity is generally increased.
- Proteinuria.
  - Usually parallels degree of hematuria
  - Rarely reaches the nephrotic range (>40 mg/m^2/h or >3.5 g/d in older children and adults)
- Microscopic urine examination.
  - Usually reveals erythrocytes and leukocytes, and granular or cellular casts.
  - Identifiable erythrocyte casts and dysmorphic erythrocytes may or may not be present, so serial urine specimens may need to be examined.
- Erythrocyte sedimentation rate usually is elevated.
- In severe oliguria, azotemia and acidosis may be seen.
- Plasma volume is usually expanded, causing a decrease in serum protein, hemoglobin, and hematocrit.
- Serum complement levels.
  - Reduced C3 in 80% of patients
  - Early in the course, reduced C4 in 50%
- Antistreptolysin O titer
  - Elevated in 80% of patients
  - Increases in titer are less common in patients who have a skin infection or who receive early treatment with antibiotics.
- Other streptococcal antibodies (anti-hyaluronidase, anti-deoxyribonuclease B) are present in 80%–90% of patients.
- Culture results are often negative for group A β-hemolytic streptococci by the time nephritis develops, particularly if antibiotics were prescribed.

IgA Nephropathy

- Findings are often typical except for abnormal urinalysis.

Benign Familial Hematuria

- All laboratory results are usually within reference range except for urinalysis.
- Presence of hematuria in otherwise asymptomatic family members suggests the diagnosis.

Alport Syndrome

- Laboratory findings
  - Reflect degree of renal impairment.
  - May vary from normal early on to advanced renal failure as disease progresses.
- Blood urea nitrogen and creatinine levels become elevated with advancing disease.
- Serum electrolytes may become abnormal.
- Hypoalbuminemia may occur in some patients who develop nephrotic syndrome.
- Serum complement level is usually normal.
- Renal biopsy may help establish the diagnosis in patients in whom the family history is unclear or in those who have a new mutation.

SLE Nephritis

- Antinuclear antibodies are positive in most.
- Anti–double-stranded DNA are positive in many patients with renal involvement.
- Serum complement components are frequently decreased.
  - Renal progression may not correlate with changes in serologic markers.
- Renal disease may be characterized by
  - Elevation of serum urea and creatinine levels
  - Decrease in serum albumin levels in the setting of nephrotic-range proteinuria

- Findings on urinalysis vary greatly.
  - Isolated hematuria
  - Hematuria with proteinuria
  - Nephrotic-range proteinuria
- Pyuria reflects the underlying glomerular inflammation.
- Erythrocyte, leukocyte, and renal tubular epithelial cell casts are frequently seen.
- Coombs test result positive for anemia.
- Leukopenia.
- Thrombocytopenia.
- Antiphospholipid antibodies; risk factor for thrombotic complications.

MPGN

- Blood urea nitrogen and creatinine values may be elevated at presentation.
- Albumin level may be low in severe cases.
- Anemia is common.
- Electrolyte disturbances reflect renal insufficiency.
- Serum C3 is depressed in 67%–75% of patients.
- Serum C4 level is often low in MPGN type 1.
- Urinalysis most commonly shows hematuria and proteinuria.
  - Proteinuria may reach the nephrotic range.
  - Hematuria may be macroscopic.
  - Cellular casts are common.
  - Nephritic factors are found in 80% of patients with DDD and in ≤50% with C3GN.
  - Quantification of urinary protein excretion is helpful for monitoring the course of the disease.
    - 24-hour urine collection *or*
    - Following the total protein and creatinine levels on spot urine samples
- Liver function studies may be atypical in cases related to viral hepatitis.
  - Evidence of hepatitis B virus, hepatitis C virus, and HIV infection should be sought.
  - Cryoglobulins may be elevated in cases of hepatitis C infection.

Interstitial Nephritis

- Peripheral eosinophilia may or may not be seen.
- If present, urinary eosinophils are demonstrated on Hansel stain.

IMAGING

- In general, imaging studies are nonspecific and not helpful in evaluating patients with nephritis.
- APSGN.
  - Chest radiography in patients with significant fluid retention and hypertension may reveal
    - A large heart with prominent pulmonary vasculature
    - Pulmonary edema
    - Rarely, pleural effusions
  - Ultrasonography is nonspecific, usually revealing bilaterally enlarged, echogenic kidneys.

DIAGNOSTIC PROCEDURES

- Alport syndrome
  - Renal biopsy may help establish diagnosis if family history is unclear or in patient with a new mutation.
- RPGN
  - Although characteristic clinical and laboratory features may suggest specific causative factors, renal biopsy often is indicated to diagnose and to determine extent of disease.
    - Electron microscopy of renal biopsy specimen reveals variations in the thickness of the GBM.
    - Splitting and lamellation of the lamina densa of the GBM give it a basket-weave appearance later in the course of disease.
- SLE
  - Renal biopsy is used to classify disease and should be performed in any patient with persistent hematuria or significant proteinuria and before therapy is begun.
    - It is important to remember that renal histology may change over the course of disease; patients may exhibit resolution, progression, and even change in histology.
    - Classes I and II represent mild disease.
    - Focal proliferative (class III) and diffuse proliferative (class IV) lesions indicate more severe disease and are found in the kidney biopsies of more than half of children with lupus nephritis.
    - Class V lupus nephritis, also called membranous nephritis, shares many features with idiopathic membranous nephropathy and portends a guarded prognosis.
    - Depending on the class of lupus nephritis, the physician may observe various degrees and combinations of histologic abnormalities.
    - IFM demonstrates deposition of immunoglobulins and complement components in the mesangium and along the capillary loops.

  - Dense deposits, corresponding to the immune complexes detected by immunofluorescence, are seen by electron microscopy.
  - Cellular proliferation and basement membrane thickening are also seen.
- MPGN
  - Definitive diagnosis of MPGN or the C3 glomerulopathies can only be made by kidney biopsy.
- Interstitial nephritis
  - Kidney biopsy is needed to confirm the diagnosis.
  - Interstitial edema with patchy or diffuse cellular infiltrates composed of T lymphocytes, macrophages, eosinophils, and plasma cells are seen on pathologic specimens.
  - Glomeruli are generally normal appearing in acute disease.
  - Irreversible interstitial fibrosis is seen in more severe cases and may develop within 1 week of disease onset.

TREATMENT APPROACH

- APSGN (although not RPGN) most often resolves spontaneously and is not affected by corticosteroids or immunosuppressive agents.
  - Even so, to avoid morbidity and mortality, the pediatrician must treat symptoms aggressively during the acute phase.
- Postinfectious non-streptococcal glomerulonephritis.
  - Treatment of the underlying infection often leads to remission in those with milder renal involvement.
- SLE.
  - Revised classification system of renal disease in lupus nephritis by the International Society of Nephrology and the Renal Pathology Society is widely used for interpreting renal biopsy findings and guiding therapy.
  - These patients are managed best by a team trained in dealing with all aspects of SLE.

SPECIFIC TREATMENTS

APSGN

- Most often resolves spontaneously
  - Must be aggressive in treating symptoms that occur in the acute phase of the illness.
    - Hypertension
      - Mild hypertension may resolve spontaneously.
      - More severe hypertension should be controlled with quick-acting antihypertensive agents.
    - Oliguria and resulting vascular overload
      - Diuretics
    - Pulmonary edema
    - Encephalopathy
  - Control of severe hypertension often requires one of the following medications:
    - Intravenous (IV) sodium nitroprusside.
    - Labetalol.
    - Nicardipine.
    - Fenoldopam.
    - Oral minoxidil.
    - Slower-acting, less potent antihypertensive drugs are not good initially but can be substituted once blood pressure has been acutely stabilized.
  - Occasionally, a patient develops acute kidney injury severe enough to require dialysis.
  - A 10-day course of antibiotics is usually given to eradicate any remaining group A β-hemolytic streptococci and prevent transmission of the organism.
  - Close contacts should be screened for streptococcal infection and treated if present.

RPGN

- Treatment depends on specific diagnosis, which is often determined by kidney biopsy.
- Plasmapheresis may be helpful in resistant forms of RPGN.
  - Anti-GBM antibody disease
  - Atypical forms of hemolytic uremic syndrome
  - Thrombotic thrombocytopenic purpura

SLE

- Treatment of SLE is divided into induction and maintenance phases.
- The effectiveness of therapy is indicated by changes in serologic parameters, blood chemistries, urinary protein quantitation, and complement levels.
  - The danger of overwhelming sepsis among these immunosuppressed patients is constant.
- High-dose corticosteroid therapy.
  - The mainstay of treatment but associated with considerable morbidity
- Pulse methylprednisolone.
  - Used for initial treatment of rapidly progressive lupus glomerulonephritis
- Oral or pulse IV cyclophosphamide.
  - Frequently recommended for treatment of World Health Organization class III, IV, and, sometimes, V renal disease
- Azathioprine and mycophenolate mofetil.
  - Have been used as steroid-sparing agents

- Mycophenolate mofetil.
  - Has shown promise as a remission-inducing agent substituted for cyclophosphamide, thus preventing significant side effects, particularly on fertility
    - Especially important given the predilection of SLE for young women of childbearing age.
    - The risk for infertility is even higher in males and with oral cyclophosphamide therapy.
- Cyclosporine and tacrolimus.
  - Used to induce and maintain remission
  - High risk for relapse on discontinuation of these agents
- B-cell depletion with rituximab and plasma exchange.
  - Severe and refractory patients
- Hydroxychloroquine.
  - Management of extrarenal manifestations and to maintain remission
- Angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers.
  - Used to control hypertension and decrease proteinuria
- Anticoagulation.
  - Indicated in children with thrombotic complications of lupus
- Care of the patient with SLE is a highly specialized endeavor requiring
  - Knowledge of current treatment modalities
  - Availability of highly specialized tests
  - Resources to care for a patient with a chronic, severe, life-threatening illness for which treatment with steroids often is disfiguring

Other

- Fulminant SLE nephritis, MPGN, IgA nephropathy, HSP nephritis
  - Methylprednisolone pulses frequently are given initially, followed by oral or IV cyclophosphamide, azathioprine, or methotrexate.
- IgA nephropathy
  - Suggested regimens for poor prognostic indicators
    - ACE inhibitors.
    - Angiotensin receptor blockers.
    - Long-term, alternate-day prednisone, with or without methylprednisolone pulses.
    - Control of hypertension is essential.
- Benign familial hematuria
  - No treatment is indicated.
- Alport syndrome
  - Treatment is supportive, with medical management of hypertension and complications of renal insufficiency.
  - Some studies have shown short-term efficacy of cyclosporine, ACE inhibitors, or receptor blockers to control proteinuria.
    - The effect on renal survival with these therapies remains unclear.
  - Dialysis or transplantation is instituted when medical management is no longer sufficient.
  - Audiologic screening can identify hearing impairment early for timely implementation of hearing-augmentation services.
- MPGN
  - Goal of treatment is to induce a reduction in proteinuria and inflammation and control hypertension.
    - Treatment is challenging, and therapy is controversial because of a lack of rigorous randomized controlled trials.
    - Some differences in clinical course and response to treatment may be seen according to the type of MPGN.
  - ACE inhibitors or angiotensin receptor blockers
    - Should be strongly considered to reduce proteinuria and control hypertension.
  - High-dose, long-term, alternate-day prednisone therapy.
    - Reported renal survival of 82% at 10 years and 56% at 20 years
  - Other therapies include
    - Cyclophosphamide, mycophenolate mofetil, and calcineurin inhibition with cyclosporine or tacrolimus have shown promise in small groups of patients, generally used in combination with corticosteroids.
    - Plasma exchange may be considered in children with documented deficiency of the regulatory protein complement factor H.
    - Anticomplement factor 5 therapy with eculizumab has shown some promise in improving outcomes in some patients with C3 glomerulopathy in small trials.
- Interstitial nephritis
  - Prompt ophthalmologic evaluation and treatment to preserve vision.
  - Treatment consists of eliminating the inciting agent if it can be identified.

- The role of corticosteroids in the management of acute interstitial nephritis is controversial.
  - Some studies suggest that early treatment may shorten the disease process.
  - Early treatment may improve long-term outcome in some patients.

WHEN TO ADMIT

- Severe hypertension
- Renal failure with significant electrolyte disturbances
- Congestive heart failure from volume overload
- Oliguria or anuria
- Rapidly progressive renal failure

WHEN TO REFER

- Acute glomerulonephritis with significant complications
- Acute glomerulonephritis that is not following a typical course expected of APSGN
- Failure of complement level to normalize within 6–8 weeks in suspected acute glomerulonephritis
- Rapidly progressive course
- Glomerulonephritis with the development of nephrotic syndrome
- Persistent hematuria and proteinuria
- Persistent hypertension
- Elevated creatinine level for age
- Family history of renal failure or deafness
- Any chronic glomerulonephritis

PROGNOSIS

- APSGN
  - For most children, the critical period is early in the illness when potentially fatal hypertension or fluid overload presents a danger.
  - Nephrotic-range proteinuria or extensive crescents by biopsy portend a poor prognosis.
  - >95% of children recover.
    - Gross hematuria resolves within 1–3 weeks.
      - Microscopic hematuria may persist for >1 year (~5% of children).
    - Proteinuria generally resolves by 3 months but can last >1 year (~7%).
    - 3% have persistent hypertension.
    - 0.9% have persistent azotemia.
    - Complement levels should normalize by 6–8 weeks.
  - Some patients with severe involvement, evidenced by nephrotic-range proteinuria or the presence of extensive glomerular crescents on biopsy, have some residual damage or may progress to end-stage renal failure.
  - Recurrences of APSGN are rare.
- HSP nephritis
  - Most children have mild renal involvement and recover within 3–6 months.
- IgA nephropathy
  - 10%–30% are anticipated to progress to renal failure over the course of several decades.
  - Poor prognostic signs include
    - Higher amounts of proteinuria
    - Presence of hypertension
    - Azotemia
    - Renal insufficiency at presentation
    - Evidence of glomerulosclerosis, crescents, or tubulointerstitial fibrosis on renal biopsy
- Alport syndrome
  - Renal disease and hearing loss are progressive.
    - ~90% of males with X-linked Alport syndrome develop end-stage renal failure by age 40 years.
      - Persistent microscopic hematuria is found early in all affected male patients.
    - Females are less severely affected, with ~12% reaching end-stage renal failure by age 40 years and 30% by age 60 years.
  - Families carrying large DNA deletions or stop codons leading to truncated proteins may be at risk for more severe disease than those with mutations leading to amino acid substitution.
    - Age at renal failure tends to run true within families, although there are exceptions.
  - ~15% of patients receiving a kidney transplant develop anti-GBM antibodies, leading to loss of the transplant in 3%.
- SLE nephritis
  - Survival rates are 90%–100% at 5 years and 94% at 11 years.
  - End-stage renal disease in 9% at 11 years of follow-up.
  - Patients with diffuse proliferative lesions on biopsy have the poorest renal outcomes.
  - Other predictors of poor renal prognosis include
    - Sclerosis on biopsy specimens
    - Hypocomplementemia
    - Decreased renal function
    - Nephrotic-range proteinuria
    - Persistent hypertension
- MPGN
  - Long-term outcome is poor.
  - 50% reach end-stage renal failure within ~11 years of diagnosis.
  - 90% reach end-stage within 20 years.

- Poor prognostic indicators include
  - Nephrotic-range proteinuria
  - Renal insufficiency
  - Hypertension
  - Necrosis, sclerosis, tubulointerstitial fibrosis on biopsy examination
- Type 1 MPGN has a better prognosis than the other 2 types.
  - Progression may be halted if the underlying cause can be addressed.
  - Long-term outcomes in C3GN subset are not yet known.
- High risk for recurrence after renal transplantation.
- Visual impairment develops over time in 10% of patients.

■ Interstitial nephritis

- The combination of interstitial nephritis with severe glomerulonephritis has a much more guarded prognosis, as combined involvement reflects greater severity of renal disease.
- Interstitial inflammation tends to heal by fibrosis, damaging segments of the remaining kidney.
-

REFERENCE

1. Modified from Couser WG. Rapidly progressive glomerulonephritis: classification, pathogenetic mechanisms, and therapy. *Am J Kidney Dis.* 1988;11(6):449–464. Copyright © 1988, Elsevier, with permission

DEFINITION

- Syndrome with clinical findings of
  - Heavy proteinuria
  - Hypoalbuminemia
  - Edema (often frank anasarca)
  - Hyperlipidemia
- Nephrotic syndrome may result from underlying systemic disease or manifest as a primary idiopathic renal disorder.

SIGNS AND SYMPTOMS

- Gradual or more acute edema and inappropriate weight gain.
  - Periorbital edema when arising in the morning.
    - Resolves during the day
    - Often mistaken for allergy
  - Clothing may be tight.
  - Socks may leave indentations in the skin of shins and ankles.
- The abdomen may be distended, and a fluid wave may be discernible on examination.
- Breath sounds may be decreased at lung bases due to accumulation of pleural fluid.
- May note
  - Gallop on auscultation of the heart
  - Rales over the lung fields
  - Hepatomegaly
- Boys may develop significant scrotal swelling.
- Girls may develop labial swelling.
- Oliguria.
  - Dark, amber-colored, concentrated-appearing urine.
  - Urine appears to foam when voided.
- Hypertension (in 16%).
  - Marked hypertension suggests underlying glomerulonephritis.
- Specific features (or associations) based on histological type of nephrotic syndrome include
  - Minimal change nephrotic syndrome (MCNS), also known as *lipoid nephrosis* or *nil disease,* is the most common pathologic diagnosis in nephrotic children.
    - Very mild microhematuria in ~13%
      - Hypertension in 10%–20%.
      - Relapses are common, but long-term prognosis is excellent.
  - Membranous nephropathy.
    - Rare in children and adolescents (1% of children with nephrotic syndrome).
    - Spontaneous remissions occur in most, but remission may not occur for several years.
    - 18%–25% of affected children develop chronic kidney disease.

DIFFERENTIAL DIAGNOSIS

- Histologic variants of primary nephrotic syndrome include
  - MCNS
  - Focal segmental glomerulosclerosis (FSGS)
  - Diffuse mesangial hypercellularity
  - Membranoproliferative glomerulosclerosis (MPGN)
  - Membranous nephropathy
- Causes of secondary nephrotic syndrome include
  - Inherited diseases
    - Congenital nephrotic syndrome
    - Diffuse mesangial sclerosis
    - Alport syndrome (always associated with significant microhematuria or gross hematuria, which precedes the development of nephrotic syndrome)
    - Nail-patella syndrome
    - Lowe (oculocerebrorenal) syndrome
  - Vasculitides
    - Lupus nephritis
    - Henoch-Schönlein purpura nephritis
    - Wegener granulomatosis
    - Goodpasture syndrome
  - Postinfectious
    - Poststreptococcal
    - HIV
    - Hepatitis B and C
    - Malaria
    - Syphilis
    - Intrauterine infections
    - Other viruses and bacteria
  - Drugs and toxins
    - Nonsteroidal anti-inflammatory drugs (NSAIDs)
    - Gold
  - Diabetes mellitus (rare in children)
  - Paraneoplastic syndrome
  - Hodgkin disease
- Mutations of certain genes are implicated in the development of hereditary forms of the nephrotic syndrome.
  - Congenital nephrotic syndrome presents in the first 3 months of life.
    - Finnish type is an autosomal-recessive disorder caused by mutations in the *NPHS1* gene encoding nephrin or the *NPHS2* gene encoding podocin (podocyte membrane protein).

- Diffuse mesangial sclerosis.
  - May be part of Denys-Drash syndrome
  - Onset <2 years with rapid progression to end-stage kidney failure, male pseudohermaphroditism, and Wilms tumor
  - Associated with mutations of the *PCLE1* gene (isolated form) or *WT1* gene (Denys-Drash syndrome)
- Nephrin and podocin mutations.
  - Also found in steroid-resistant, autosomal-recessive, and sporadic cases of FSGS in infants and older children, with rapid progression to renal failure.
  - *PCLE1* and *WT1* mutations may also be associated with some cases of sporadic FSGS.
  - Mutations in the *ACTN4* gene encoding α-actinin result in an autosomal-dominant form of FSGS, with onset during early childhood and slow progression to renal failure.
  - Variants of the *MYH9* gene have been associated with increased risk for FSGS and progression to end-stage kidney disease in African Americans.

LABORATORY FINDINGS

- Urinalysis is the first test to be done in a child with edema.
  - Significant proteinuria.
  - Significant microscopic hematuria or gross hematuria.
    - Up to 25% of children with primary nephrotic syndrome will have 3–5 erythrocytes per high-power field.
  - Glycosuria suggests underlying tubular injury and may be seen with FSGS.
- Serology.
  - Blood urea nitrogen and creatinine values are generally within reference range or only slightly increased in primary MCNS.
  - Serum albumin level is low.
  - Mild hyponatremia may be present.
  - Total calcium levels are low; ionized calcium levels are usually within reference range.
  - Serum cholesterol level is usually increased.
  - Third component of complement is generally within reference range.
    - A low level suggests MPGN, poststreptococcal glomerulonephritis, or lupus nephritis.
  - Hepatitis B, hepatitis C, and HIV are associated with forms of nephrotic syndrome and should be investigated in high-risk patients. HIV is associated with collapsing FSGS.
- Antinuclear antibody testing.
  - Older children
  - Children with signs and symptoms suggestive of systemic lupus erythematosus
- Tests to quantify urinary protein losses.
  - 24-hour urine collection.
    - Nephrotic-range proteinuria = urinary protein excretion >40 mg/m^2/h or 1 g/m^2/d in children
  - In incontinent children, urine protein to creatinine ratio on a first morning urine sample.
    - Ratio (mg/mg) >2:1 on a random urine sample is considered nephrotic.
  - Urinary protein quantification is helpful for monitoring partial response to treatment of children with resistant forms of nephrotic syndrome.
- Genetic testing.
  - Role is evolving to test for mutations of genes encoding proteins involved in podocyte structure and function (*NPHS1, NPHS2, PLCE1*) and transcription factor Wilms tumor.

IMAGING

- Chest radiography
  - Usually shows small cardiac silhouette and, in severe cases, pleural fluid.
  - Cardiomegaly may be seen in patients with increased intravascular volume.

DIAGNOSTIC PROCEDURES

- Kidney biopsy
  - Recommended for older children who are at higher risk for causes of nephrotic syndrome other than minimal change disease and those resistant to steroid therapy

TREATMENT APPROACH

- Nephrotic syndrome occurring in the first 2 years of life should be evaluated and managed with a pediatric nephrologist.
- Clinical response to corticosteroids is informative in determining long-term outcome.
  - 85% of nephrotic children respond to a trial of prednisone.
    - 94% will have responded by 4 weeks of initiating therapy.
  - Biopsy findings do not predict which children with MCNS will be corticosteroid resistant or which with FSGS will be responsive.

- Patients who achieve remission on steroids (whether they have MCNS or FSGS) do not progress to renal failure if they remain responsive to corticosteroid therapy.

- Children aged 1–6 years (most likely to have MCNS) with new onset of typical, pure nephrotic syndrome should be given a trial of corticosteroids.
  - Depending on the treatment regimen, 36%–61% of children will have a relapse within first year of initial episode.
    - Relapse = first morning urine test ≥2+ for protein by albumin test sticks *or* urine protein to creatinine ratio >2 for 3 consecutive days.
    - Relapses are usually triggered by intercurrent illnesses or allergies.
    - Parents can be taught to use albumin test sticks or sulfosalicylic acid at home to monitor urinary protein excretion.
- Children who have repeated relapse while corticosteroids are being tapered or within 2 weeks of completing a course of corticosteroids are considered corticosteroid dependent and may develop steroid toxicity.
  - Second-tier therapies for difficult cases should be discussed with a pediatric nephrologist.
- Children who fail to respond to initial or subsequent courses of corticosteroids have corticosteroid-resistant nephrotic syndrome and a more guarded prognosis.
  - Consult with a pediatric nephrologist for consideration of a renal biopsy and more aggressive treatment.
- Salt intake should be restricted in edematous children.
- Water intake should be restricted only if
  - Significant hyponatremia develops.
  - Edema is intractable.
- Diuretics should be used judiciously.
- Treatment of membranous nephropathy is controversial.
  - High rate of spontaneous remission
  - Consider treatment with high-dose corticosteroids (oral or intravenous [IV]), alone or combined with cytotoxic agents, mycophenolate mofetil, cyclosporine, and rituximab if the patient has
    - Renal insufficiency
    - Persistent heavy proteinuria
    - Hypertension
    - Sclerosis on biopsy
- Treatment for congenital nephrotic syndrome includes
  - Supportive, but must be aggressive
  - Until kidney transplantation can be done, treatment may include
    - Intensive nutritional support
    - Angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) to decrease proteinuria
    - Prostaglandin inhibitors to decrease glomerular filtration rate and, therefore, proteinuria
    - Nephrectomy
    - Maintenance on dialysis

SPECIFIC TREATMENTS

Corticosteroids

- Prednisone, 2 mg/kg daily or 60 mg/m^2 daily (maximum, 60 mg/d) for 6 weeks as treatment of initial episode of nephrotic syndrome
  - Usually given in divided doses
  - Can also be given as a single morning dose
    - Followed by single dose of 1.5 mg/kg or 40 mg/m^2 (maximum, 40 mg/d) for an additional 6 weeks given in the morning on alternate days.
    - Most recent recommendations call for discontinuation of treatment at this point, without taper.
- Treatment of relapse
  - Prednisone, 2 mg/kg daily or 60 mg/m^2 daily until urine is trace or negative for protein for 3 consecutive days.
  - Dose is then changed to 1.5 mg/kg or 40 mg/m^2 on alternate days for 4 weeks.
- Complications of high-dose and long-term corticosteroid therapy
  - Development of cushingoid features
  - Cataract formation
  - Glaucoma
  - Gastritis
  - Peptic ulcer disease
  - Pancreatitis
  - Hypokalemia
  - Hypertension
  - Increased risk of infection
  - Behavioral changes
  - Hyperlipidemia
  - Bone disease

- Growth delay if corticosteroid treatment is prolonged
  - Growth impairment should lead to consideration of use of steroid-sparing agents.
  - Supplemental vitamin D may prevent some bone loss, especially in early treatment.
  - Bone mineral density should be measured with prolonged exposure.
  - Use of gastrointestinal prophylaxis with a proton pump inhibitor should be considered when prescribing high doses.

Other Pharmacologic Agents

- ACE inhibitors or ARBs
  - Can be tried in resistant nephrotic syndrome, even in the presence of normotension.
  - High doses of ACE inhibitors may decrease progressive sclerosis.
- Diuretics
  - Furosemide, alone or in combination with a thiazide diuretic, is used to treat clinically significant edema.
  - IV albumin followed by IV furosemide when edema is severe
    - Interferes with ambulation
    - Compromises respiratory status
    - Causes tissue breakdown
  - Renal function and urine output are fairly well maintained.
  - Patients must be monitored closely during infusion for signs of intravascular overload.
    - Rales
    - Cardiac gallop
    - Hepatomegaly
  - Treatment can be used in the severely edematous, corticosteroid-resistant nephrotic patient, in whom cyclosporine therapy is being considered, for improvement of renal perfusion and prevention of acute renal failure.

Secondary/Tertiary/Complementary Treatment for Difficult Cases

- Cyclophosphamide, chlorambucil
  - Can induce prolonged remission
  - Not as successful in the setting of corticosteroid resistance as other therapies
  - Complications/toxicity of cytotoxic agents include
    - Increased risk of infection.
    - Cancer.
    - Sterility, with higher doses than those typically used for nephrotic syndrome and after repeated or prolonged courses.
    - Hemorrhagic cystitis (cyclophosphamide); encourage large fluid intake and frequent voiding.
    - Seizures (chlorambucil).
- Cyclosporine or tacrolimus
  - Can be used as a corticosteroid-sparing agent in patients who do not respond to an alkylating agent.
  - Complications include
    - Acute and chronic renal injury
    - Acute renal failure in severely nephrotic patients on cyclosporine who have markedly decreased intravascular volume
  - Relapse after withdrawal is common.
- Methylprednisolone infusions
- Mycophenolate mofetil
  - Some success as a corticosteroid-sparing agent
  - Complications include
    - Bone marrow suppression
    - Gastrointestinal upset
- ACE inhibitors or ARBs
  - Can be tried in resistant nephrotic syndrome, even in the presence of normotension, to decrease urinary protein excretion.
  - ACE inhibitors act by decreasing glomerular capillary pressure and can cause a reversible increase in serum creatinine and hyperkalemia that must be monitored.
  - High doses of ACE inhibitors may decrease progressive sclerosis.
- NSAIDs
  - Complications include
    - Acute renal failure in children with significantly decreased intravascular volume
    - Salt retention and edema
    - Risk of renal failure, especially in patients with decreased intravascular volume

WHEN TO ADMIT

- Initial episode for teaching of parents, especially if complications are present
- Anasarca interfering with ambulation or compromising ventilation
- Pleural effusions or ascites interfering with ventilation
- Signs of volume overload (congestive heart failure)
- Infection (eg, severe cellulitis, peritonitis)
  - Parenteral antibiotic treatment
- Significant hypertension
- Significant electrolyte abnormalities
- Compromised renal function
  - May require dialysis to manage edema, electrolyte disturbances, and uremia

WHEN TO REFER

- Complicated nephrotic syndrome
- Outside the expected age range (<1 year or >10 years)
- Accompanied by signs of glomerulonephritis (renal insufficiency, hypertension, hematuria, hypocomplementemia)
- Refractory edema
- Frequently relapsing nephrotic syndrome
- Corticosteroid-dependent nephrotic syndrome
- Corticosteroid-resistant nephrotic syndrome

COMPLICATIONS

- Infections
  - Spontaneous bacterial peritonitis.
  - Sepsis.
  - Cellulitis.
  - Pneumonia.
    - Children with recurrent nephrotic syndrome should receive 23-valent and heptavalent conjugated pneumococcal vaccination.
  - *Streptococcus pneumoniae* and gram-negative bacteria are responsible for most infections in nephrotic syndrome.
  - Predisposing factors for the development of bacterial infections include
    - Tissue edema
    - Immunosuppressive therapies
- Thromboembolism
  - Deep-vein thrombosis.
  - Pulmonary embolism.
  - Renal-vein thrombosis.
  - Dural sinus thrombosis.
  - Arterial thrombosis.
  - Risk factors include
    - Age ≥12 years at diagnosis
    - Higher degrees of urinary protein loss
  - Contributory factors include
    - Increased plasma levels of procoagulant factors
    - Urinary loss of inhibitors of coagulation
    - Thrombocytosis
  - Predisposition to thrombus formation may be exacerbated by decreased intravascular volume, especially in the face of vigorous forced diuresis.
  - Children with thromboembolism are more likely to have a secondary as opposed to primary forms of nephrotic syndrome.
- Hyperlipidemia
  - In unremitting nephrotic syndrome, abnormal plasma lipid levels may contribute to cardiovascular morbidity; treatment of lipid abnormalities should be considered.

PROGNOSIS

- ~25% of children with MCNS, who have relapse, follow a frequently relapsing course, ie, either
  - ≥2 relapses within 6 months of completing an initial course of corticosteroids *or*
  - ≥4 relapses within 1 year
- Prognosis of congenital nephrotic syndrome.
  - Depends on the underlying cause
  - Guarded for congenital nephrotic syndrome of the Finnish type, with significant morbidity and mortality from complications
    - Malnutrition
    - Infection
    - Thrombotic events caused by a prothrombic state from massive protein losses
- FSGS prognosis.
  - Complete remission is achieved in only one-fourth of children treated with corticosteroids.
  - ≤50% may progress to end-stage renal disease (ESRD).
    - A subgroup will progress rapidly within 3 years of presentation.
    - Recurrence in ≤40% of patients in end-stage disease who receive a renal transplant.
- MPGN has a poor prognosis.
  - 50%–67% of patients develop nephrotic syndrome.
  - 50% of patients develop ESRD by 11 years of diagnosis and 90% within 20 years.
- Membranous nephropathy, poor prognostic factors include
  - Persistent heavy proteinuria
  - Persistent hypertension
  - Elevated serum creatinine level
  - Significant scarring on biopsy

DEFINITION

- Neural tube defects (NTDs) are a group of congenital anomalies resulting from failure of the neural tube to close between the third and fourth week of fetal development.
- Most NTDs can be divided into cranial presentations and spinal presentations.
  - Cranial presentations include anencephaly and encephalocele.
  - The most common spinal presentations include
    - Spina bifida occulta, a bony anomaly
    - Combined bony and neural anomalies: myelomeningocele, meningocele, myeloschisis, congenital dermal sinus, lipomatous malformations, diastematomyelia, and caudal agenesis
- "Open" NTDs represent failure of the neural tube to close during primary neurulation.
  - Anencephaly, encephalocele, and myelomeningocele
- "Closed" NTDs result from impaired secondary neurulation.
  - Diastematomyelia, meningocele, lipomatous malformations, teratomas, dermal sinus tracts, and tethered spinal cord
- *Spina bifida* is a collective term used to describe a group of congenital anomalies of the vertebrae, meninges, and spinal cord.
  - *Spina bifida occulta* refers to incomplete development of the vertebrae, with spinal cord and overlying skin remaining intact.
  - *Meningocele* is a form of spina bifida in which meninges protrude into a cystic sac of cerebrospinal fluid (CSF) with no nerve involvement.
  - *Myelomeningocele* is a disruption of the vertebrae with protrusion of the meninges and spinal cord.
    - The most severe type of spina bifida.
- In diastematomyelia the spinal cord is split into two along its axis; each hemicord is surrounded by its own dural sac.
  - Often associated with spina bifida and scoliosis
- Lipomatous malformations, the most common closed NTDs, occur when excessive lipomatous tissue is within or attached to the spinal cord or the filum terminale.
  - Presentations vary in involvement of spinal cord, including
    - Lipoma of the filum terminale
    - Lumbosacral lipoma
    - Lipomyelocele

PHYSICAL EXAMINATION

Diagnostic Approach

- Complete neurologic examination is imperative at initial presentation and subsequent evaluations.
  - Head circumference
  - Functional motor assessment
    - Impairment level does not always correspond to the anatomic level of the lesion.
    - May not be symmetric.
  - Sensory assessment
- Spinal deformity, lower extremity deformity, anal sphincter tone, and urinary stream should also be assessed.

Signs and Symptoms

- Open NTDs usually are apparent on physical examination.
- Closed NTDs may not be apparent at birth.
  - Often have an associated cutaneous abnormality over the defect, including
    - Peri-spinal lipomas
    - Hemangiomas
    - Tufts of coarse hair
- Symptoms that may present later in life can include
  - Lower extremity asymmetry
  - Weakness
  - Lower back pain
  - Bladder or bowel dysfunction
- Chiari II malformation associated with myelomeningocele.
  - Symptoms may occur at any age but most commonly in infancy.
  - Most common clinical manifestations are related to swallowing.
    - Choking on foods
    - Frequent vomiting
  - Signs of brain stem dysfunction.
    - Repeated aspiration pneumonia
    - Apnea or cyanotic spells
    - Inspiratory stridor
    - Vocal cord paralysis
    - Hoarse or high-pitched cry
  - In older children signs and symptoms may include
    - Weakness or spasticity of the extremities
    - Headaches caused by hydrocephalus
    - Neck pain
    - Cerebellar dysfunction
    - Oculomotor changes
    - Scoliosis

- Anencephaly.
  - Poorly differentiated brain stem
  - No differentiated supratentorial neural matter
- Encephalocele.
  - Defect of the skull (usually in the occipital region) that can result in herniation of meninges and brain tissue

Physical Examination

- Physical examination is critical because lesion level on imaging may not accurately correlate with functional level.
- Deep tendon reflexes and motor movement evaluation can help identify functional level.
- The motor examination should focus on movements against gravity.
- Often, parents are able to report accurate sensory levels that may be difficult to elicit on examination.
- It is important to note any asymmetry and to document the functional level of the lesion accurately (**Tables 1** and **2**).

LABORATORY EVALUATION

Laboratory Findings

- Diagnosis prior to birth.
  - Screening with maternal serum α-fetoprotein is most accurate between the 16th and 18th week of gestation.
- Obtain the following values at birth to evaluate renal function:
  - Urinalysis
  - Urine culture
  - Serum urea nitrogen
- Repeat routinely, especially for children who have vesicoureteral reflux or any signs or symptoms of a urinary tract infection (UTI).

IMAGING

- Spina bifida.
  - Imaging for central nervous system (CNS) pathology begins during the neonatal period.
    - Repeated as necessary for assessment of associated conditions

Table 1. Deep Tendon Reflex Site

Deep Tendon Reflex Site	Nerve Root
Biceps	C5-6
Brachioradialis	C5-6
Triceps	C6–C8
Patellar	L2–L4
Achilles	S1-2

Table 2. Motor Movement Against Gravity and Correlative Nerve Root

Motor Function	Nerve Root
Hip flexion	L1-2
Hip adduction	L2-3
Hip abduction	L4-5
Knee extension	L3-4
Knee flexion	L5–S1
Ankle dorsiflexion, foot inversion	L4-5
Foot eversion, great toe dorsiflexion	L5–S1
Ankle plantar flexion	S1-2

- Open NTDs.
  - Detection with fetal ultrasound is highly specific in the hands of a skilled ultrasonographer.
- Magnetic resonance imaging (MRI) is obtained at some centers prenatally.
  - Used to predict lesion level and evaluate for intracranial pathology or other structural anomalies
- Hydrocephalus.
  - Computed tomography (CT) or ultrasound for diagnosis and monitoring
- Ventricular shunt and suspected shunt malfunction.
  - CT scan of the head and radiograph of shunt tubing is essential.
- Chiari II malformation.
  - May also reveal defects in cellular migration in the cerebral cortices
- Spinal cord tethering or syringomyelia.
  - MRI of the spine
- A baseline MRI of the brain and spine.
  - Helpful for comparison in future investigations
  - Especially in progressive neurologic deterioration
- Plain radiographs.
  - Evaluation for scoliosis, kyphosis, and dislocation of the hips.
  - Inaccurate for hip studies in patients <4–6 months; evaluate with ultrasound in this age group.
- Pain that may represent pathologic fracture.
  - Ultrasound and radiographs

TREATMENT APPROACH

- Management of NTDs requires a multidisciplinary team approach.
- Because of the complexity of associated secondary conditions, the team may include
  - Neurosurgeons
  - Orthopedic surgeons
  - Urologists
  - Neurologists
  - Physiatrists
  - Developmental pediatricians
  - Nurses
  - Social workers
  - Dietitians
  - Therapists
  - One individual acting as the advocate and treatment coordinator

SPECIFIC TREATMENT

Neurosurgical Management

- Fetal surgical closure has shown potential benefits in some children in multicenter trials.
- On delivery, open NTDs should be immediately covered with a saline-moistened dressing to avoid rupture of the sac or drying of exposed neural placode.
- Examine neonate in prone or lateral recumbent position to avoid placing pressure on the defect.
- Meningitic doses of broad-spectrum antibiotics should be started promptly.
- Surgical closure of the defect is usually performed within 72 hours after birth.
  - Removal of the malformed sac
  - Creation of a barrier between the spinal canal and the exterior
  - Restoration of typical CSF environment around the spinal cord
- Operative mortality during repair of the primary defect is extremely rare.
- Hydrocephalus and shunt placement.
  - After NTD is surgically closed, the ventricles often enlarge, leading to hydrocephalus.
    - Some neonates already have significant hydrocephalus at birth.
  - A ventricular shunt is placed in 80%–90% of all cases.
  - Timing of shunt placement is straightforward with clinical and radiologic evidence of hydrocephalus.
  - Once the shunt is placed, the goal becomes keeping the shunt functioning optimally.
  - The rate of shunt revision is high; ~40%–50% of all infants with NTDs require a shunt revision in the first year of life, ~10% every year thereafter.
  - Endoscopic third ventriculostomy is an alternative to a ventricular shunt in certain cases.
- Myelomeningocele.
  - Orthopedist should be involved in treatment, as paralysis, muscle imbalance, and spasticity produce orthopedic deformities that often require surgical correction.
  - Following initial surgical repair, the terminal spinal cord is commonly embedded in scar tissue.

- Tethered cord syndrome is a stretch-induced functional disorder of the spinal cord where an inelastic structure anchors caudal portion of the cord.
  - Essentially all children with repaired myelomeningocele have a tethered spinal cord.
- Untethering is reserved for individuals who have progressive symptoms.
- Release of tethered cord may offer improvement or stabilization of neurologic function, urologic dysfunction, and orthopedic deformities.
- The cord can re-tether, so a multidisciplinary team is important in deciding to repeat an untethering procedure.

- Chiari II malformation is commonly associated with myelomeningoceles but is symptomatic enough to require surgery in 15%–35% of cases.

Urologic Management

- All patients should have urinary function monitored.
  - Bladder function is often affected to varying degrees, though level of lesion is not explicitly predictive of bladder function.
- Goals are preservation of kidney function and attainment of bowel and bladder continence.
  - 10%–15% of all children with myelomeningoceles are continent of urine.
  - Urodynamic monitoring of storage and leak point pressures is key to preservation of renal function and attainment of social urinary continence.
  - Social continence may be achieved by the use of intermittent catheterization.
    - Successfully eliminates urine from the bladder, mimicking normal voiding
    - Decreases infection and reduces the effects of hostile bladder pressure on the kidneys
- In poor bladder compliance or uninhibited contractions
  - Medication (eg, anticholinergic agent, oxybutynin [Ditropan]) may improve bladder compliance and decrease storage pressure.
  - Some individuals who are unresponsive to anticholinergic medication and catheterization may benefit from operative intervention.
    - Procedures are tailored to each individual but may include
      - Vesicotomy
      - Augmentation
      - Cystoplasty
      - Catheterisable stoma (Mitrofanoff)
      - Slings
      - Artificial urinary sphincters

Bowel Management

- Attaining and sustaining bowel continence is a complex issue in spina bifida.
  - In thoracic-level spina bifida, there is often difficulty in bearing down.
  - With sacral lesions patients may have difficulty achieving appropriate stool consistency.
- Constipation.
  - Common and results from factors such as
    - Diet
    - Lack of exercise and mobility
    - Anticholinergic medications
    - Neurologic bowel dysfunction
- Can exacerbate bladder function problems and become a risk factor for UTI.
- Oral medications can be used to control consistency.
- Bowel-emptying techniques are the cornerstone of stool continence in spina bifida.
  - Goals should include having soft, formed stools on a daily basis.
  - Bowel emptying techniques include
    - Behavioral training
    - Rectal stimulation
    - Suppositories
    - Enemas
- Certain patients may benefit from surgical intervention.
  - Cecostomy or a Malone procedure, in which a conduit is created to the proximal colon.
  - This stoma is used for administration of antegrade colonic enemas.

Orthopedic Management

- In the absence of severe developmental delay and hypotonia, ambulation is highly dependent on sensorimotor functional level.
- Strong hip flexors, adductors, and quadriceps are needed to ambulate.
  - Independent mobility is likely for almost all cases of low lumbar and sacral lesions.
  - For lesions above L2, independent mobility is unlikely; parents should anticipate wheelchair use.
- As some children age, ability to ambulate often declines because of increasing weight and orthopedic deformity.
- Spinal deformities in myelomeningocele, such as scoliosis and kyphosis, are exceedingly common.
- Hip dislocations frequently occur but do not always require treatment.
- Severe foot deformities are seen in ≤80% of children.

- Early physical therapy is critical for optimal motor function.
  - Goals of physical therapy should include
    - Normalization of experiences
    - Improvement of posture for sitting or standing
    - Management of orthotics
      - Commonly used to prevent contractures
      - Aid in minimizing energy expenditure to maintain mobility
    - Prevention of skin breakdown
  - Range of motion exercises are essential at any age.
- If feasible, a standing program should be instituted at an early age.
- Specialized equipment, such as walkers, braces, standers, and parapodiums, may be needed for support and mobility.
- Occupational therapy is often needed for hydrocephalus because of high incidence of visual-motor and visual-perceptual difficulties.
- Families should participate in the development of an individualized education program with school personnel.
- For adolescents with NTD receiving special education services, transition plans should begin <14 years to
  - Address shift to vocational and occupational domains.
  - Assist families in transition from childhood to adulthood.

WHEN TO REFER

- Evidence of raised intracranial pressure, such as vomiting or changes in mental status.
- Symptoms of spinal cord tethering.
- Recurrent UTIs.
- Renal calculi or impairment.
- All patients should be referred to a multidisciplinary clinic with specialists in development, genetics, neurosurgery, nursing, nutrition, orthopedics, orthotics, social work, therapy (occupational and physical), and urology.
- Referral to early intervention and physical therapy are essential during the neonatal period.
- All children 0–3 years of age with NTDs should be referred to an early intervention program.
- Children entering school should be referred to their school district preschool program for formal evaluation of cognitive functioning.

FOLLOW-UP

- Throughout infancy and early childhood, patients are followed with routine renal and bladder ultrasounds.
- Routine voiding cystourethrograms to assess bladder size, shape, and capacity and identify urethral reflux.
- Regular urodynamic studies assess the function of the bladder and urethra to
  - Determine if neurologic lesion has changed.
  - Determine if spinal cord tethering has occurred.
  - Map urologic treatment course.

COMPLICATIONS

Developmental and Cognitive

- The range of developmental outcomes in individuals with NTDs is extensive.
- In general, cognitive function is often higher for
  - Children with lower lesions.
  - Children who do not experience CNS infections (ventriculitis or meningitis).
  - Individuals without associated hydrocephalus; cognitive function is commensurate with same-aged peers.
- Myelomeningocele.
  - 80% have intelligence within the normal range.
  - Often have specific learning disabilities.
- Hydrocephalus.
  - Nonverbal learning disorders, found more often in children with myelomeningocele who have stronger language skills and weaker visual perceptual and visual-motor skills
  - Corresponding academic skills include
    - Stronger reading decoding and spelling skills
    - Weaker mathematics and reading comprehension skills
    - Often have difficulty with attention and executive function
    - Often have increased risk of attention-deficit/hyperactivity disorder
- Routine neuropsychologic and psychoeducational evaluations for children with spina bifida ensure that all learning issues are identified.

Dermatologic

- Spina bifida
  - Impaired sensation leads to increased rate of skin breakdown and pressure sores.
  - Intervention for early signs of inflammation is imperative.
  - Protect insensate skin with properly fitted orthotics and shoes, wheelchair push-ups, and time out of the wheelchair.
  - As children mature, they should be taught to check for evidence of pressure sores daily.

Latex Allergy

- Allergies to latex are more common in this population; reactions can vary from mild to anaphylaxis.
- Beginning at birth, latex precautions should be in place for patients with myelomeningocele.
- Latex avoidance in children with spina bifida has been demonstrated to prevent latex sensitization and latex allergy.

PROGNOSIS

- There has been a tendency for prenatal counseling to be unduly negative, failing to recognize the heterogeneity of NTDs and effect of contemporary postnatal medical and surgical management.
- Prognosis for all NTDs is largely dictated by
  - Anatomic site
  - Extent of CNS tissue involvement
  - Coexisting conditions
- Long-term prognosis for survival is less optimistic if
  - Associated syndrome
  - Brain tissue herniation
  - Repeated CNS infection
- In children with myelomeningocele, prognosis for survival can be improved by
  - Optimal shunt function.
  - Preservation of kidney function.
  - In older patients these are the most common, and potentially preventable, causes of death.

PREVENTION

- The periconceptional use of daily supplements containing 0.4 mg of folic acid has been shown to prevent 40%–80% of cases of spina bifida and anencephaly.
- Counseling provided to women with a previous NTD-affected pregnancy and supplementation with 4.0 mg of folic acid have been demonstrated to substantially reduce risk of recurrent NTDs.
- Countries that have implemented mandatory folic acid food fortification programs have significantly reduced the prevalence of NTDs.

DEFINITION

- A heterogeneous group of conditions in which abnormalities of skin and nervous system predominate.
- Prototypical neurocutaneous conditions include
  - Neurofibromatosis (NF)
  - Tuberous sclerosis
  - Von Hippel-Lindau (VHL) disease
- Several other genetic or developmental anomaly syndromes share the phenotypic association of cutaneous and neurologic abnormalities.
  - Sturge-Weber syndrome (SWS)
  - Ataxia-telangiectasia (A-T)
  - Incontinentia pigmenti
  - Hypomelanosis of Ito
  - Epidermal nevus syndromes
- NF is divided into 8 subtypes.
  - NF1 and NF2 are different conditions with only minimal overlap.
    - Both are autosomal-dominant disorders with high penetrance but variable phenotypic expression.
  - Type 1: NF1 (von Recklinghausen disease).
    - Complex disorder with neurologic, cutaneous, skeletal, vascular, and endocrinologic abnormalities.
    - Neurofibromas (benign tumors).
    - Tumors appear in late childhood and grow in response to hormonal changes.
    - Tumors proliferate with age and may compromise local function by mass effect.
  - Type 2: NF2.
    - A tumor syndrome defined by the presence of bilateral vestibular schwannomas
    - Also known as *multiple inherited schwannomas, meningiomas,* and *ependymoma syndrome*
  - Type 3 (variant) and type 4 (atypical).
    - Autosomal dominant
    - Not used clinically
    - Resemble NF2
    - More cutaneous NFs
    - Greater risk of optic gliomas, neurilemmoma, meningiomas
  - Type 5: segmental NF.
    - Skin lesions are located on a single body segment (eg, leg).
    - Somatic mosaicism.
  - Type 6: familial café au lait macules (CALMs).
    - CALMs are the only disease manifestation.
    - Requires 2 generations to diagnose.
  - Type 7 (late onset): schwannomatosis.
    - Symptoms manifest in the 20s.
    - Multiple schwannomas.
    - No vestibular or intradermal schwannomas.
  - Type 8 (not otherwise specified): not clinically used.
- Tuberous sclerosis complex (TSC) or Bourneville disease.
  - Autosomal-dominant multisystem disorder
  - Characterized by perturbed cellular growth and differentiation in the brain, heart, kidneys, skin, eyes, and other tissues
- SWS or encephalotrigeminal angiomatosis.
  - Rare sporadic disorder.
  - Characterized by
    - Upper facial port-wine stain (PWS)
    - Ipsilateral ocular abnormalities
    - Ipsilateral leptomeningeal angiomatosis
  - Only one or two of the triad features may be present.
  - Leptomeningeal involvement is defining element.
- VHL disease is an autosomal-dominant multi-organ familial cancer syndrome.
  - Subtype 1
    - High risk for hemangioblastoma, renal cell carcinoma (RCC), pancreatic cyst or tumor
    - Low risk for pheochromocytoma
  - Subtype 2a
    - High risk for hemangioblastoma, pheochromocytoma
    - Low risk for RCC, pancreatic cyst or tumor
  - Subtype 2b
    - High risk for hemangioblastoma, RCC, pheochromocytoma, pancreatic cyst or tumor
  - Subtype 2c
    - High risk for pheochromocytoma
    - Low risk for hemangioblastoma, RCC, pancreatic cyst or tumor
- A-T or Louis-Bar syndrome.
  - Autosomal-recessive progressive neurodegenerative disorder

SIGNS AND SYMPTOMS

NF1

- Characteristic lesion is the neurofibroma.
  - Proliferation of Schwann cells and fibroblasts
- Small neurofibromas appear as
  - Pink to flesh color to brown papules.
  - Soft, spongy texture.
  - Gentle downward pressure can cause these lesions to sink through the underlying dermis and create a dimple.

- Size and number vary greatly.
- Slight predilection for trunk involvement, but neurofibromas can occur anywhere on the body.
- Plexiform type (seen in ~50% of patients).
  - Variant of neurofibroma
  - Can be large
  - Can cause considerable disfigurement
  - Highly variable masses
    - Sometimes soft and spongy in texture; other times, feels like a bag of rope
  - May have surface hyperpigmentation or remain flesh colored
  - Overlying skin
    - May be somewhat thickened
    - May exhibit increased hair growth
  - Often produce soft tissue masses
- Earliest features often are CALMs.
  - Tan, oval macules.
  - Smooth margins.
  - No surface texture change.
  - Remain flat.
  - No increased hair growth.
  - May vary in size and shape.
  - May increase in number and size with age.
  - Axillary or inguinal freckling is seen in almost 90% of NF1 patients, usually developing between 3 and 5 years of age.

NF2

- Characteristic vestibular schwannomas lead to progressive deterioration of hearing.
  - Bilateral in almost all patients by age 30 years
- Often under-recognized in children with ocular or cutaneous findings, or meningioma, presenting in the first few years of life.
  - An increasingly recognized early presentation is mononeuropathy, often with any of the following characteristics:
    - Persistent facial palsy
    - Squint
    - Hand or foot drop
- Patients may develop
  - Intracranial or spinal meningiomas
    - ~50% of patients.
    - Lifetime risk may be as high as 75%.
    - May be the presenting feature, particularly in childhood.
  - Ependymomas
    - Spinal intramedullary tumors, often multiple, are usually ependymomas.
  - Astrocytomas
  - Neurofibromas
  - Schwannomas of the cranial, spinal, and peripheral nerves
  - Cutaneous schwannomas (with minimal clinical effect)
- Ependymomas and astrocytomas are seen in ≤33% of patients.
- Peripheral schwannomas may arise from any nerve.
  - May produce pain or sensory or motor dysfunction
- Patients may develop peripheral neuropathy not related to tumor growth.
- Seizure disorders are uncommon.
- Cognitive impairment is not a feature.
- Ocular findings include
  - Juvenile posterior subcapsular lens opacities
  - Retinal hamartomas
  - Epiretinal membrane
  - Cortical wedge opacities

TSC

General

- Classic triad in 29% of patients, and 6% lack all 3 symptoms.
  - Seizures
  - Intellectual disability
  - Facial angiofibromas
- Seizures and facial lesions occur frequently.
- Intellectual function often is normal or only slightly impaired.
  - ~50% of patients with TSC have normal intelligence.
  - ~30% have profound intellectual disability.
- Hallmark of TSC is the development of hamartomas in the various organ systems involved.
- An international consensus conference in 1998 revised diagnostic criteria, based on new understanding of disease and its underlying pathophysiological features.[1]
  - Major criteria
    - Facial angiofibroma or forehead plaque
    - Ungual or subungual fibroma
    - >3 hypomelanotic macules
    - Connective tissue nevus (shagreen patch)
    - Cortical tuber (When cortical dysplasia [tuber] and cerebral white matter migration tracks are both present, they count as 1 criterion rather than 2 criteria.)
    - Subependymal nodule
    - Subependymal giant-cell astrocytoma
    - Multiple retinal hamartomas
    - Cardiac rhabdomyoma
    - Renal angiomyolipoma
    - Lymphangiomyomatosis

- Minor criteria
  - Dental enamel pits
  - Hamartomatous rectal polyps
  - Bone cysts (radiographic evidence sufficient)
  - Cerebral white matter migration lines (When cortical dysplasia [tuber] and cerebral white matter migration tracks are both present, they count as 1 criterion rather than 2 criteria.)
  - Gingival fibromas
  - Retinal achromic patch
  - Nonrenal hamartomas
  - Multiple renal cysts
  - Confetti skin lesions

- Diagnosis for TSC.
  - Definitive: 2 major, or 1 major and 2 minor criteria
  - Probable: 1 major criterion plus 1 minor criterion
  - Possible: 1 major or ≥2 minor criteria
- TSC has no pathognomonic feature.
- Individual features may occur in isolation.
  - Primary care physician must consider the diagnosis of TSC only if
    - >1 organ system is involved *or*
    - Different lesion types occur in a single system.
- Central nervous system (CNS) manifestations are the most common and often most disabling aspect of TSC.
- Neurologic features include
  - Seizures
  - Cognitive disability
  - Behavioral disturbances

Seizures

- Occur in 80%–90% of patients.
- All types of seizures except classic absence seizures have been reported.
- Infantile spasms.
  - Seen in approximately one-third of infants with TSC.
    - The presenting feature in 70% of infants.
    - Thorough description of the clinical and electroencephalographic findings in infantile spasms is found in Seizure Disorders.
    - Children with infantile spasms are likely to have intellectual disability.

Cognitive Impairment

- Seizure onset and severity are closely associated with severity of cognitive impairment.
  - Early onset of seizures or infantile spasms is associated with poor cognitive outcome.
- Most patients with TSC and cognitive disability have epilepsy.
  - Many patients with TSC and seizures have normal intellect.
- Presence of ≥7 cortical tubers on magnetic resonance imaging (MRI) confers a 5-fold increase in risk of moderate to profound cognitive impairment.
  - A few patients with multiple tubers and normal intellect have been reported.
- Autism spectrum disorder (ASD) is common in TSC.
  - Prevalence estimates range from 17%–68%.
  - ASD is much more common in children with intellectual disability in TSC (>60%), compared with only 6% among TSC children with typical cognitive function.
  - Almost all children with ASD and TSC have epilepsy.
  - Patients with ASD and TSC do not exhibit the male preponderance seen in ASD without TSC.
  - TSC is found in ≤4% of children with ASD.
  - TSC is the underlying genetic condition in 14% of children with ASD and seizures.

Behavioral Abnormalities

- Behavioral abnormalities include
  - Severe temper tantrums
  - Restlessness
  - Impulsivity
  - Attention-deficit/hyperactivity disorder (ADHD)
  - Self-injury
  - Anxiety
  - Depression
- Among children with TSC and a history of infantile spasms and ASD, 69% exhibit behaviors disruptive to the family by 5 years of age.
- Anxiety disorder is seen in ≤59% of adults.
- Depression is seen in 35% of adults.
- Learning disabilities have been noted frequently in TSC.
  - No systematic studies are available to date.

Neuropathology

- Neuropathologic findings responsible for many of the symptoms of TSC include
  - Tubers
  - Subependymal nodules
  - Subependymal giant cell astrocytomas
- Cortical tubers are nodular areas of gray and white matter dysplasia.
  - Often seen on the apex of a gyrus.

- Tubers are present in >95% of patients with TSC.
- Tubers have been noted as early as 20 weeks' gestation.
- Known to persist throughout life.
- No risk of malignant degeneration exists.
- Tubers function as epileptogenic foci.

■ Subependymal nodules are present in ≤80% of patients with TSC.
- Arise from the lateral and third ventricle walls
- Often protrude into the lumen
- Can be present before birth
- Sometimes may be noted on imaging studies during infancy
- Not correlated with severity of neurologic symptoms, unlike tubers

■ Subependymal giant cell astrocytomas may be symptomatic.
- Occur in ≤14% of patients with TSC
- Seem to arise from subependymal nodules
- Continue to grow during childhood
- May produce focal neurologic deficits or obstructive hydrocephalus

Cutaneous Manifestations

■ Skin findings are the most consistent features and often the earliest signs of TSC.
- Hypomelanotic macules
  - Found in >90% of patients with TSC.
  - Formerly known as *ash leaf spots*.
  - May be present at birth.
  - In light-skinned individuals, may be visible only with a Wood lamp.
  - Usually >1 cm.
  - Have a characteristic leaf shape: oval with one blunt end and one pointed end.
  - At least 3 lesions must be visible for diagnostic significance.
  - Seen most commonly on the trunk but may occur anywhere.
  - Fine, stippled hypopigmentation on the extremities, known as *confetti lesions*.
  - When hypomelanotic macules occur on hair-bearing surfaces, associated poliosis (white hair) may be found.
- Facial angiofibromas
  - Noted in 70%–75% of individuals.
  - Formerly known as *adenoma sebaceum*.
  - Small, discrete, shiny pink to reddish papules develop by ~5 years of age.
  - Increase in number and size into the teenage or early adult years.
  - Initially distributed over the malar areas.
  - Often spread to chin and nasolabial folds during puberty.
- Forehead plaques
  - Flesh-colored to erythematous fibrotic plaques on the forehead or frontal scalp in ~19% of patients with TSC
  - Appear later than angiofibromas
- Shagreen patches
  - Connective tissue nevi seen in 20%–50% of patients with TSC
  - Flesh colored
  - Slightly raised
  - Irregularly shaped plaques
  - Prominent follicles
  - Cobblestone texture
  - Most often on the lower back
  - Usually noted in later childhood
- Ungual and subungual fibromas
  - Firm flesh-colored to red papules that develop beside or beneath the nails.
  - Lesions under the nail may appear as a longitudinal ridge or groove.
  - Toenail involvement is more common.
  - Typically appear during puberty.

Cardiac Manifestations

■ Cardiac rhabdomyomas are present in 50%–70% of neonates with TSC.
- Usually remain asymptomatic
- Often multiple and decrease in size over time
- Often diagnosed on prenatal ultrasound
- The most common finding in neonates diagnosed with TSC in the first week of life

Ocular Manifestations

■ Retinal astrocytic hamartomas
- Seen in 50%–87% of patients with TSC.
- Most remain asymptomatic.
- May be bilateral in ≤50%.
- 3 clinical types include
  - Raised mulberry-like calcified nodule
  - Flat translucent gray patch
  - Transitional lesion with mixed features

■ Factors that may lead to loss of vision include
- Involvement of the macula
- Enlargement of the hamartoma
- Vitreous hemorrhage
- Retinal detachment

■ Other ocular findings may include
- Retinal pigment anomalies
- Strabismus
- Cataracts

- Colobomas
- Iris depigmentation
- Eyelid angiofibromas

Renal Manifestations

- Renal lesions are the second most common organ system involvement in TSC (after CNS disease).
  - Angiomyolipomas are found in 55% of 7-year-olds and 80% of 18-year-olds with TSC.
  - Renal cystic disease develops in 50% of patients.
  - Prevalence increases with age.
- Bilateral and multiple tumors are common.
- Small lesions may remain asymptomatic.
- Lesions >4 cm pose risks of
  - Severe hemorrhage
    - Risk ranges from 25%–50%.
    - 20%–30% of these patients present to emergency departments in shock.
    - Risk is much higher with aneurysms >5 mm in diameter.
  - Hypertension
  - Renal insufficiency
- Renal cysts occur in ~17% of children and 47% of adults with TSC.
- Solitary epithelial cysts are the most common.
- ~3%–5% of patients with TSC will develop polycystic kidney disease as a contiguous gene deletion syndrome.
  - *TSC2* gene is adjacent to the adult polycystic kidney disease gene *PKD1* on chromosome 16.
  - ~2% will have severe, early-onset polycystic disease.
  - Polycystic kidney disease may lead to renal insufficiency in late adolescence.
- Renal disease may escalate after acute kidney injury.
  - Toxic reaction to anticonvulsant or nonsteroidal anti-inflammatory drugs
  - After prolonged seizures

Pulmonary Manifestations

- Symptomatic lymphangiomyomatosis occurs in 1%–2% of patients with TSC, almost exclusively in young women.
- Radiographic evidence of lymphangiomyomatosis may be seen in 26%–39% of women.
- Main clinical findings include
  - Spontaneous pneumothorax
  - Dyspnea
  - Cough
  - Hemoptysis

Vascular Manifestations

- Arterial dysplasia seen most often in renal angiomyolipomas
- Also has been reported with basilar artery and aortic aneurysms

Dental Manifestations

- Gingival fibromas occur in ~50% of adults with TSC.
- Almost all patients with TSC have dental enamel pits in permanent teeth.
  - Dental pits rarely cause problems.
- Extensive fibromas may result in malocclusion or abnormal tooth eruption.

SWS

General

- Exhibits at birth
- Upper facial capillary malformation (PWS), involving the area of skin innervated by the ophthalmic (V1) division of the trigeminal nerve
  - Area includes
    - Forehead
    - Brow ridge
    - Upper eyelid
    - Possibly the lower eyelid
  - Lower areas of the face (V2 or V3 distributions) also may be involved.
    - No apparent significant risk of SWS exists in the absence of V1 involvement.
  - Unilateral PWS is the rule.
    - Only 10%–30% have bilateral PWS.
    - With unilateral facial PWS, the risk of SWS is ~8%.
    - If bilateral PWS is present, the risk is much higher.
  - One of the more useful clinical clues seems to be eyelid involvement, a significant predictor of disease.
  - PWSs are pink to red blanching macules to patches with variable irregularity of the borders.
    - They are capillary malformations.
    - Remain fixed in location.
    - Show no tendency to evolve or involute over time.
    - Growth should be commensurate with the child's growth.
    - With age, the PWS may thicken and darken, becoming somewhat cobblestoned by adulthood.

Ocular Manifestations

- May include
  - Glaucoma

- Vascular anomalies of the globe
  - Conjunctiva
  - Episclera
  - Retina
  - Choroid
- Buphthalmos
- Iris heterochromia
- Retinal detachment
- Retinal pigment degeneration
- Cataract
- Optic disc coloboma

- Glaucoma is the most common ocular problem.
  - Occurs in ≤70% of patients.
  - Usually ipsilateral to the PWS.
  - May be bilateral, even if the PWS is unilateral.
  - Glaucoma may develop from birth to the fifth decade.
  - Median age at onset is 5 years.
  - Develops in infancy to early childhood in 60%.
  - Development in infancy, when the globe is more sensitive to increased intraocular pressure, may lead to
    - Increased corneal diameter
    - Buphthalmos
    - Iris heterochromia
  - Choroidal hemangioma ipsilateral to the PWS is seen in ≤71% of patients.
  - Over time, retinal changes can lead to visual field defects and vision loss.

Neurologic Manifestations

- Neurologic features may include
  - Seizures
  - Focal neurologic deficits
  - Hemiparesis
  - Developmental delay
  - Progressive intellectual disability
  - Headaches
- Seizures are the most common neurologic problem.
  - Occur in 75%–83% of patients.
  - ~75% of seizure disorders develop in the first 2 years of life.
  - Partial motor seizures are the most common type (40%).
  - Generalized tonic-clonic, atonic, and absence seizures may also occur.
  - Infantile spasms may be the presenting seizure type.
  - Seizures tend to worsen with age, becoming more frequent, severe, and complex.
  - Seizures may be provoked by febrile episodes.
  - Status epilepticus may occur in up to half of these children.

Developmental and Behavioral Problems

- Developmental delays are seen in up to half of patients.
  - Early milestones often normal.
  - Decline in function noted over time.
  - Some of the cognitive decline occurs during periods of encephalopathy after prolonged or severe seizures.
  - Others experience decline in function as a result of recurrent stroke-like episodes.
  - Factors that seem to correlate best with developmental delay and its severity are presence of
    - Bilateral cerebral lesions
    - Degree of cerebral atrophy
    - Presence of intractable seizures
    - Multiple seizure types
    - Early onset of seizures (controversial)
  - In the absence of seizures, cognitive development is normal.
  - 85% of patients with seizure onset >4 years have normal intelligence.
- Psychological manifestations of SWS may include
  - ADHD
  - Irritability
  - Social problems
- Inattentive and oppositional behaviors may be noted.
- ~85% of patients who have intellectual disability exhibit emotional or behavioral problems.
  - Aggressive behavior toward others
  - Self-abuse
- Headache, including migraine, is seen in 30%–45%.
  - Median age at onset is 8 years.
  - Migraines may be associated with
    - Visual aura
    - Visual field defects

VHL

General

- Most common tumors are
  - Cerebellar
  - Spinal
  - Retinal hemangioblastomas
- Other associated tumors include
  - Renal cysts
  - RCC
  - Pheochromocytoma
  - Pancreatic cysts
  - Neuroendocrine tumors
  - Endolymphatic sac tumors of the inner ear
  - Cystadenomas of the epididymis or broad ligament

- Slow-growing tumors or retinal tumors are commonly the first symptomatic lesions of VHL.
  - Symptoms are largely attributable to mass effect or obstructive hydrocephaly.
  - Although histologically benign, these CNS lesions are a major source of mortality in VHL.

CNS Manifestations

- CNS hemangioblastomas are the most common tumors in VHL (60%–84%).
  - Occur most commonly in the cerebellum (63%).
    - Followed by the spinal cord (32%) and
    - Brain stem (5%)
  - Mean age at presentation is 33 years.
    - Tumors may develop in childhood (<10 years) through the fourth decade of life.
  - Cerebellar tumors may present with
    - Headache
    - Nausea
    - Vomiting
    - Vertigo
    - Slurred speech
    - Broad-based gait
  - Clinical signs may include
    - Papilledema
    - Nystagmus
    - Ataxia
    - Dysmetria
  - Spinal hemangioblastomas may produce
    - Back pain
    - Numbness
    - Pain or weakness in arms or legs
    - Posterior column proprioceptive defects
    - Incontinence
  - CNS hemangioblastomas tend to exhibit alternating periods of growth and stability.
    - Low-level chronic symptoms may worsen acutely during a critical growth phase.

Ocular Manifestations

- Retinal hemangioblastomas (capillary hemangiomas) develop in more than half of patients with VHL.
  - Most have solitary tumors.
  - Approximately one-third have multiple lesions.
  - Half of patients have bilateral retinal tumors.
    - Most develop in the second to third decades of life.
  - Mean age at diagnosis is 25 years.
  - Retinal tumors may develop at any time from infancy to the ninth decade.
  - Patients may experience painless loss of visual acuity or visual field defects.
  - They may remain asymptomatic.
  - Exudation or hemorrhage from the hemangiomas may lead to
    - Macular edema
    - Retinal detachment
  - Secondary changes in the anterior chamber may lead to
    - Glaucoma
    - Cataract

Renal Manifestations

- Renal cysts are seen in approximately one-half of patients.
- Often multiple and bilateral.
- May remain asymptomatic but are considered premalignant.
- Stable lesions may not require intervention.
- RCC develops in 75% of patients by age 60.
- RCC is seen in patients with type 1 or type 2b disease.
  - Typical histologic type is clear cell.
  - Usually develops >20 years.
  - Often earlier than with sporadic renal carcinoma.
  - Lesions often are multiple and bilateral.
  - Tumors may be associated with cysts.
  - May have better 10-year survival than sporadic RCC.
- Symptoms may include
  - Hematuria
  - Flank pain
  - Flank mass
- By the time symptoms develop, metastases are present in 30%–50% of patients.

Endocrine System

- Pheochromocytoma may be the presenting feature of VHL.
  - Severe hypertension or hypertensive crisis is the most frequent presentation.
  - Occurs in 10%–24% of persons with type 2 disease.
  - May be the only manifestation of VHL (type 2c).
  - VHL accounts for ~20% of all pheochromocytomas.
  - Mean age at presentation is 27 years.
  - Tumors may be present even <10 years.
  - Pheochromocytoma in VHL differs from sporadic tumors by
    - Occurring at an earlier age
    - Developing multiple, bilateral, and extra-adrenal tumors
  - Only 5% of VHL pheochromocytomas are malignant.

- Clinical features may include
  - Hypertension (paroxysmal or sustained)
  - Palpitations
  - Sweating
  - Flushing
  - Headache
  - Tachycardia
  - Pallor
  - Nausea
- Pancreatic cysts or tumors occur in ~35%–77% of patients with VHL.
  - Most are benign.
- Benign cystadenomas occur in ~12% of patients with VHL.
- ~9%–17% of patients with VHL develop neuroendocrine tumors.
  - May be multifocal
  - May metastasize in 10%–20% of patients
- Mean age at diagnosis of pancreatic lesions is 29–38 years.
- Islet cell tumors may be seen as early as 10 years of age.
- Most pancreatic lesions are asymptomatic and found during routine imaging surveillance.
  - Malignant tumors have been reported in ≤50% of patients.
- ~10% will develop endolymphatic sac tumors.
  - Locally invasive cystadenomas arising from the inner ear labyrinth ectoderm may cause
    - Hearing loss that is irreversible and presents at average of 22 years
    - Tinnitus
    - Vertigo
  - Facial nerve and vocal paralysis may result from progressive tumor growth.
- Cystadenomas may develop in the epididymis in men and the uterine broad ligament in women.
  - Usually asymptomatic

A-T

- Consanguinity is common.
- Characteristic features include
  - Progressive decline in cerebellar function
  - Oculocutaneous telangiectasia
  - Immunodeficiency
  - Susceptibility to cancer
  - Sensitivity to ionizing radiation
- Infants are normal.
  - Begin to walk at ~12 months of age.
  - By age 2–3 years, develop unsteady gait and staggering.
  - Choreoathetosis begins soon thereafter.
    - Dystonia or choreoathetosis develops in 90% of patients.
- By age 10 years, most require wheelchairs for mobility; they have slow reflexes and tend to fall.
- Ocular apraxia develops in early childhood.
  - Difficulty with voluntary eye movement.
  - May be confused with absence seizures in infants.
  - Dysarthric speech often is present early in childhood.
    - Can be difficult to assess
- Telangiectasias (tortuous dilated capillaries) develop several years after the onset of neurologic symptoms on
  - Bulbar conjunctiva
  - Nasal bridge
  - Ears
  - Neck
  - Knuckles
  - Antecubital and popliteal fossae
- Immunodeficiency varies.
  - May be severe in approximately one-third of patients.
  - Many patients have reduced numbers of T lymphocytes with poor mitogen response.
  - Low serum levels are noted despite normal to high numbers of B cells.
    - Immunoglobulin E (IgE) (80% of patients)
    - IgG_2 (80%)
    - IgA (60%)
  - IgM levels vary widely, at times rising enough to create a hyper-viscous state.
  - Some patients exhibit poor immune response to pneumococcal polysaccharides.
  - Patients with severe immunodeficiency may develop recurrent sinopulmonary infections.
  - Opportunistic organisms are not a problem in patients with A-T.

DIFFERENTIAL DIAGNOSIS

NF1

- CALMs are often the earliest presenting feature (**Table 1**).

TSC

- Does not have a pathognomonic lesion.
- Fulfillment of diagnostic criteria is of paramount importance.
- Facial angiofibromas once were considered diagnostic.
  - Now known to occur in multiple endocrine neoplasia type 1

Table 1. Differential Diagnosis of Multiple Café au Lait Macules

Condition	Other Clinical Features	Comment
Typical		≤25% of typical individuals may have 1–3 CALMs. ≤40% of people with >6 CALMs and no other symptoms never progress to NF1.
NF1	Axillary freckling, cutaneous NFs, plexiform NFs, Lisch nodules, optic glioma, bony abnormalities, positive family history	Present in 95% of patients with NF1; must have >6 CALMs (>5 mm before puberty; >15 mm after puberty).
NF1-like syndrome	Axillary freckling, multiple CALMs, macrocephaly; no neurofibromas or Lisch nodules	Also called Legius syndrome; caused by *SPRED1* mutation; may have learning disability.
Hereditary nonpolyposis colon cancer syndrome	Axillary freckling, multiple CALMs, cutaneous neurofibromas; colon cancer at early age	Homozygous form, usually with consanguinity
Watson syndrome	Pulmonic stenosis, ID, axillary freckling	Axillary freckling only in NF1 and Watson syndrome type 1
Albright syndrome	Polyostotic fibrous bony dysplasia, precocious puberty, hyperthyroid, Cushing syndrome	Usually large-segment CALM with irregular border ("coast of Maine")
Silver-Russell syndrome	Short stature, skeletal asymmetry, abnormal pubertal development	CALMs and small achromic macules have been reported but are not constant features.
Bloom syndrome	Malar facial erythema and telangiectasia; photosensitivity; long, narrow face with prominent nose; short stature; hypogonadism; malignancy risk	Facial photosensitivity with multiple CALMs triggers evaluation.
Tuberous sclerosis	Hypopigmented macules, facial and periungual angiofibromas, seizures, ID, renal and cardiac hamartomas	Hypopigmented macules more common; mixture very concerning for tuberous sclerosis complex
Noonan syndrome	Hypertelorism, webbed neck, short stature, leg lymphedema, pulmonic stenosis, hypogonadism	CALMs may be seen in 15% of patients with Noonan syndrome.

Abbreviations: CALM, café au lait macule; ID, intellectual disability; NF, neurofibromatosis; NF1, neurofibromatosis 1.

Adapted from American Academy of Pediatrics. *Pediatric Dermatology: A Quick Reference Guide.* Mancini AJ, Krowchuk DP, eds. 3rd ed. Elk Grove Village, IL: American Academy of Pediatrics; 2016; and Spitz JL. *Genodermatoses: A Clinical Guide to Genetic Skin Disorders.* 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2005.

- Patients with *TSC2* mutations are more likely to present with infantile spasms, developmental delay, and angiofibromas and often have more severe disease.
- Patients with *TSC1* mutations more often present with family history or hypomelanotic macules and may have less severe disease.
- Patients with no identified mutation are more likely to present with renal angiomyolipomas.

SWS

- Isolated (ie, nonsyndromic) facial PWS
  - Unilateral forehead PWS has no underlying syndrome in 92% of patients.

- Bilateral PWS has a much higher likelihood of association with SWS.

- Wyburn-Mason syndrome
  - Rare disorder consisting of retinal and CNS arteriovenous malformations associated with upper facial PWS
  - Symptoms include
    - Headaches
    - Seizures
    - Focal neurologic deficits
    - Retinal hemorrhage
    - Subarachnoid hemorrhage

VHL

- CNS hemangioblastomas create symptoms by mass effect.
- Similar to many other tumors, cysts, and obstructive hydrocephalus.
- Evaluation of mass effect with neurologic symptoms should reveal characteristic radiologic findings of hemangioblastomas.
- Differential diagnosis of retinal capillary hemangiomas in VHL disease is shown in **Table 2**.
- Differential diagnosis of renal cysts includes the diagnosis of polycystic kidney disease.
- Pheochromocytoma may occur sporadically or in the setting of
  - VHL
  - Multiple endocrine neoplasia type 2a or 2b with associated medullary thyroid carcinoma
  - NF
  - Succinate dehydrogenase subunit mutations

A-T

- The differential diagnosis of A-T is provided in **Table 3.**

DIAGNOSTIC APPROACH

NF1

- Cannot be diagnosed clinically until ≥2 of the major diagnostic criteria are met.[2]
  - >6 CALMs
    - >5 mm in prepubertal child
    - >15 mm after puberty
  - Axillary or inguinal freckling
  - ≥2 neurofibromas of any type or ≥1 plexiform neurofibroma
  - Optic pathway glioma
  - ≥2 Lisch nodules of the iris
  - Characteristic bony lesion: sphenoid wing dysplasia, or thinning of the cortex of long bones—with or without pseudoarthrosis
  - First-degree relative with NF1

- History.
  - Should include questions about
    - Developmental milestones
    - Learning
    - Language
    - Social skills
    - Emotional and behavioral functioning, particularly self-esteem
  - Family history is of paramount importance in the initial evaluation of a child with CALMs only.
- Physical examination.
  - Should start with a thorough skin survey for CALMs
  - Thorough examination of the entire skin surface should also reveal the presence of plexiform neurofibromas.
    - May be present at birth
    - May develop in the first few years of life
- Evaluation for possible NF1 depends on age.
  - Many features develop over time.
  - CALMs are present at birth and will increase in size and number for the first 5–7 years.
  - Bowing of the long bones (especially tibia) and cutaneous plexiform neurofibromas typically are visible within the first year of life.
  - Axillary and inguinal freckling, optic gliomas, and scoliosis may not be apparent until age 7 years.
  - Cutaneous neurofibromas and iris Lisch nodules usually appear during or after the teenage years.

NF2

- History should include
  - Vision or hearing changes
  - Tinnitus
  - Vertigo
  - Gait disturbances
  - Decreased facial sensation
  - Facial weakness or twitching
  - Hoarseness
  - Dysphagia
  - Headaches
- Family history of NF2 is crucial for diagnosis.
- Definite NF2.[3]
  - Bilateral vestibular schwannomas *or* first-degree relative with NF2 *plus*
    - Unilateral vestibular schwannomas *or* any 2 of the following characteristics:
      - Meningioma
      - Schwannoma
      - Glioma

Table 2. Differential Diagnosis of Retinal Capillary Hemangioma in von Hippel-Lindau Disease

Condition	Feature	Presence of Retinal or Subretinal Exudates
von Hippel-Lindau disease	Orange-red circumscribed tumors Pair of prominent vessels Stellate macular exudates	Yes
Coats disease	Diffuse retinal vascular anomaly	Yes
Wyburn-Mason syndrome	Dilation and tortuosity of retinal arteries and veins but no intervening hemangioma	No
Retinal cavernous hemangioma	Cluster of small dilated vessels around central vein Lack of prominent feeder vessels	No
Vasoproliferative tumor of the retina	Pink to yellow retinal tumor Lack of dilated feeder vessels Lack of stellate macular exudates	Yes (non-stellate)

Derived from Magee MA, Kroll AJ, Lou PL, Ryan EA. Retinal capillary hemangiomas and von Hippel-Lindau disease. *Semin Ophthalmol.* 2006;21(3):143–150.

Table 3. Differential Diagnosis of Ataxia-Telangiectasia

Condition	Neurologic Features	Presence of Telangiectasia	Increased α-Fetoprotein	Cancer Risk	Immune Deficiency	Sensitivity to Radiation
Ataxia-telangiectasia	Early ataxia, oculomotor apraxia, progressive neurologic decline	Yes	Yes	Yes	Yes	Yes
Ataxia-telangiectasia-like disorder (*hMRE11* mutation)	Ataxia early	No	No	No	No	Yes
Nijmegen breakage syndrome	Microcephaly, intellectual disability	No	No	Yes	Yes	Yes
Ataxia oculomotor apraxia type 1	Early ataxia, progressive neurologic decline	No	No	No	No	No
Ataxia oculomotor apraxia type 2	Late-onset ataxia	No	Yes	No	No	No

Adapted from Chun HH, Gatti RA. Ataxia-telangiectasia, an evolving phenotype. *DNA Repair (Amst).* 2004;3(8–9):1187–1196; Perlman S, Becker-Catania S, Gatti RA. Ataxia-telangiectasia: diagnosis and treatment. *Semin Pediatr Neurol.* 2003;10(3):173–182; and Taylor AM, Byrd PJ. Molecular pathology of ataxia telangiectasia. *J Clin Pathol.* 2005;58(10):1009–1015.

        - Neurofibroma
        - Juvenile posterior subcapsular cataract
- Probable NF2.[3]
    - Unilateral vestibular schwannoma *plus* any 2 of the following characteristics:
        - Meningioma
        - Schwannoma
        - Glioma
        - Neurofibroma
        - Juvenile posterior subcapsular cataract
    - *Or* multiple meningiomas *plus* unilateral vestibular schwannoma
    - *Or* any 2 of the following characteristics:
        - Schwannoma
        - Glioma
        - Neurofibroma
        - Juvenile posterior subcapsular cataract
- Physical examination should focus on
    - Vision.
    - Hearing.
    - Cranial and peripheral nerve function.
    - Younger patients often have
        - Headache
        - Tinnitus
        - Cranial nerve symptoms
        - Skin or spinal tumors before the onset of hearing loss
    - Eye examination should assess the presence of lens opacities.
    - Cranial nerve examination should specifically address
        - Trigeminal nerves
        - Facial nerves
        - Auditory nerves
    - Neurologic examination should assess
        - Balance
        - Gait
        - Deep tendon reflexes
    - At the skin examination, the physician should note the presence of
        - Neurofibromas
        - CALMs
        - Cutaneous schwannomas
            - Present in approximately one-half of patients.
            - May be subcutaneous nodules or plaques with thickened texture and occasional hair growth.
            - May be surface pink to flesh-colored papules.

TSC

- History.
    - In infants, seizures often are the first symptom.
    - Any infant with new-onset seizures should have a detailed history, including
        - Skin lesions
        - Developmental milestones
        - Family history
    - Initial examination should include
        - Wood lamp examination of the entire skin surface
        - Funduscopic examination for hamartomas
        - Thorough neurologic examination
    - Older children should be screened for
        - Seizure disorder
        - Developmental delay
        - ASD
- Delay of TSC diagnosis is not uncommon.
    - In a review of 243 records by Staly and colleagues, 81% were diagnosed by 10 years; however, 39% of patients had earlier diagnostic findings.
    - The most commonly missed presenting features were seizures and skin lesions.

SWS

- Infants with facial PWS on the forehead and eyelids should be evaluated for the possibility of SWS.
- Evaluation should include ophthalmologic examination.
    - If eye findings or any other typical clinical features, such as seizures, are present, neuroimaging is mandatory.
- Routine MRI may be performed even in the absence of seizures.
- History.
    - Earliest manifestation is the PWS present at birth.
    - Relevant history in a child with facial PWS includes
        - History of seizures
        - History of eye or vision problems
        - Concerns about development
    - Older children should be asked about
        - Headaches
        - Vision changes
        - Episodes of weakness
        - School progress
- Physical examination.
    - Should include a thorough eye examination.
        - Clues to early glaucoma.
            - Difference in sizes of cornea or globe
            - Iris heterochromia
        - Presence of PWS on eyelids should be noted.

  - Auscultation of the orbits, fontanels, and temples should be performed to detect bruits.
  - Funduscopic examination may reveal the characteristic "ketchup stains" of choroidal angiomas.
  - Tortuous vessels or colobomas should be noted.
- Neurologic examination should search for focal deficits.
- Developmental evaluation is important.
  - Particularly if the child has a seizure history
- Observation of an infant should specifically address the presence of a head turn or early handedness.
  - Potential clues to visual field cuts

VHL

- Diagnosis established in a patient who has
  - One characteristic tumor and positive family history
  - Hemangioblastoma *plus* one other tumor when the family history is negative
- History
  - Most important historical information is family history.
    - 80% of cases are familial.
  - Changes in vision.
  - Development of neurologic symptoms.
    - Clumsiness
    - Broad-based gait
    - Hearing loss
    - Slurring of speech
    - Pain
    - Numbness or weakness in limbs
    - Loss of bowel or bladder control after complete toilet training
  - Hematuria or flank pain.
  - Heart palpitations.
  - Flushing.
  - Sweating spells.
  - Episodic nausea and vomiting.
- Physical examination should include
  - Regular blood pressure evaluation
  - Thorough eye examination
  - Thorough neurologic examination with particular attention to cerebellar and spinal functions
  - Observation of gait
  - Test of balance
  - Test of deep tendon reflexes
  - Test for sensation

A-T

- Earliest manifestation of A-T is the ataxia.
  - Begins as broad-based gait or staggering
  - Evident by age 2–3 years
- Any other history should focus on
  - Additional neurologic symptoms
  - Developmental milestones
- Additional history should include
  - Presence of neurologic problems
  - Consanguinity in the family
- Examination should focus on neurologic findings.
  - Cerebellar function
  - While difficult to assess in young children, voluntary visual tracking of objects will often reveal the early development of oculomotor apraxia.
  - In older children, telangiectasia may be noted on
    - Bulbar conjunctiva
    - Skin of the neck
    - Face
    - Ears
    - Extremity flexures
- Examination also should include
  - Thorough lymph node examination
  - Abdominal evaluation for hepatosplenomegaly

LABORATORY FINDINGS

NF1

- Routine laboratory testing is unnecessary if the diagnosis is firmly established.
- In cases of uncertain diagnosis or a child with only CALMs or only one criterion, test for gene mutations.
  - Complementary series of analyses is available, including
    - Premature truncation test
    - Heteroduplex analysis
    - Fluorescent in situ hybridization assay
  - This tiered analysis provides a sensitivity of 95%.
  - Genetic testing may have limited clinical value, with lack of genotype-phenotype correlation except in 2 situations.
    - Complete loss of the *NF1* gene, which portends more severe disease with severe cognitive impairment, large tumor burden, and higher risk for malignant peripheral nerve sheath tumors
    - A known small deletion in exon 17, which confers a milder phenotype without cutaneous neurofibromas

NF2

- Should always include formal audiologic testing for sensorineural hearing loss.
  - Brain stem auditory evoked response
- Once the diagnosis is established, audiometry should be repeated every 6–12 months.
  - Annual screening appropriate for
    - Children at risk
    - Asymptomatic children with a detected mutation
- Molecular genetic testing for the mutations is available on a clinical basis and should be used for relatives at risk.
  - Allows appropriate long-term screening
  - Might prevent unnecessary expensive testing

TSC

- Once diagnostic criteria are fulfilled, molecular testing can be performed to determine the specific mutation.
- 15%–20% of patients who fulfill TSC diagnostic criteria have no identifiable mutations.
- Clinical gene testing is available by using combined techniques, such as
  - Denaturing high-performance liquid chromatography
  - Heteroduplex analysis
- Mutation detection rate is only 85%, even with combined methods.

SWS

- Routine laboratory testing is not useful.

VHL

- Should begin with molecular testing for the specific mutation in the *VHL* gene
  - Phenotypic profile and tumor risk are directly related to the types of mutation.
  - Identification of *VHL* gene mutation carriers early in life is critical to determine the type of tumor risk and the necessary ongoing surveillance the child will need.
  - It is particularly important to identify those at risk for retinal disease.
    - Early detection of intraocular tumors can lead to prompt vision-saving therapy.
- Subsequent laboratory evaluation for patients with type 2 disease should consist of
  - Annual screening for plasma or urine catecholamines and metanephrine.
  - Begin at age 10 years.
  - Typical profile in VHL pheochromocytoma is noradrenergic, with norepinephrine elevations representing 98% of these patients.

A-T

- Serum α-fetoprotein.
  - Increased in >95% of patients.
  - Serum α-fetoprotein increase is only useful >2 years.
    - Some children have persistent mild increases beyond the neonatal period.
- Karyotyping rarely is typical in A-T.
  - Often shows translocations between chromosomes 7 and 14
- Quantitative immunoglobulins may show low levels of
  - IgE
  - IgA
  - IgG_2
- IgM is normal or high.
- Quantitative T- and B-cell numbers reveal
  - Low levels of T cells
  - Normal to slightly high levels of B cells
- Radiosensitivity test currently available is the colony survival assay.
  - Uses the patients' transformed lymphocytes.
  - Requires ~3 months to complete
- Gene testing is not useful unless the family mutation is known.
  - *ATM* is a huge gene with 66 exons and >400 known mutations
    - None with a frequency >3%
- Measurements of the *ATM* protein from the transformed lymphocyte cell line also is possible by immunoblotting.

IMAGING

NF1

- Routine neuroimaging usually is not undertaken.
- Evidence of scoliosis or long bone anomaly merits plain-film radiography.
  - Scoliosis may require MRI or computed tomography (CT) to
    - Define the extent.
    - Help map surgical intervention.
- Head MRI is indicated for evaluation of
  - Focal neurologic changes
  - New-onset seizures
  - Severe headaches
  - Vision changes
  - Proptosis
  - Short stature
  - Rapid change in head circumference
  - Plexiform lesions
  - Severe cognitive deficits
  - Precocious or delayed puberty

- Cranial MRI is indicated to evaluate for possible optic pathway glioma once symptoms have developed.
  - Routine imaging before symptom onset is not indicated.
  - Once optic gliomas are diagnosed, MRI should be obtained
    - Every 2 years
    - With any symptom change to age 10 years
- One unusual finding is the presence of unidentified bright objects on T2-weighted sequences of cranial MRI.
  - These lesions are present in 60%–90% of children but only ~30% of adults.
    - Their significance is uncertain.
  - Controversial evidence suggests that some learning disabilities correlate with presence and specific locations of unidentified bright objects.
- MRI is useful to assess for radiculopathy.
  - Neurofibromas have a propensity to develop along or within the spine, often impinging on nerve roots.
- MRI is the mainstay of evaluation of plexiform neurofibromas.
- Development of pain, or any focal neurologic deficit, warrants an MRI.
  - Particularly important if pain develops in a plexiform neurofibroma, where pain may herald malignant change.
- Positron emission tomographic (PET) scanning may be of more value in distinguishing benign from malignant lesions.
- Imaging is useful in evaluation of cerebrovascular disease and renal artery stenosis.

NF2

- Routine screening MRI of the brain is required for any patient with
  - Unilateral vestibular schwannoma
  - Multiple intracranial or spinal tumors
  - First-degree relative with NF2
  - Child with meningioma
- Any child at risk for NF2 should have a screening brain MRI annually beginning at age 7 years.
- Gadolinium-enhanced MRI with thin cuts through the internal auditory canals for assessment of vestibular schwannomas.
- Spinal MRI should be considered if any symptoms or neurologic deficits are noted.

TSC

- Initial imaging studies for infants with TSC include
  - Brain studies (MRI or CT)
  - Echocardiography
  - Renal ultrasound
- Cortical tubers are best evaluated by MRI.
- Subependymal nodules may be seen in infancy on MRI as T1-weighted hyperintense nodules.
  - By age 1 year, the subependymal nodules contain calcium and may be visualized with CT.
- MRI may be useful to identify subependymal giant cell astrocytomas.
  - Radiologic distinction from subependymal nodules is difficult.
- Renal lesions in older children and adults may be evaluated by ultrasound, CT, MRI, or PET.
- Chest CT is indicated for all women with TSC to evaluate for possible pulmonary lymphangiomyomatosis.

SWS

- Leptomeningeal enhancement, with or without cortical atrophy, is the radiologic hallmark of SWS.
  - Gadolinium-enhanced MRI is the most sensitive imaging modality to evaluate for leptomeningeal angiomatosis.
  - Leptomeningeal involvement is ipsilateral to the PWS.
  - May be seen before calcifications develop.
  - Calcification of adjacent gyri may give the classic "tram track" appearance seen on CT and even plain-film radiographs.
  - Involvement of the parietal and occipital lobes often is noted before frontal or temporal findings.
  - PET and single-photon emission CT may reveal areas of altered metabolism and hypoperfusion.
- Choroidal hemangioma almost always is associated with leptomeningeal lesions.
  - Makes CNS imaging mandatory
- Choroidal angiomas are best visualized with MRI.

VHL

- MRI with gadolinium contrast is the modality of choice for most features of VHL.
- Hemangioblastomas of the cerebellum are usually subpial in location.
  - May appear as a solid enhancing mass with or without surrounding fluid space.
  - May appear as a more complex tissue or fluid mass.

- Spinal hemangioblastomas are solid enhancing intramedullary masses, frequently associated with a surrounding fluid-filled syrinx that enlarges and displaces the cord.
- Renal cysts may be found on MRI, ultrasound, or CT.
- Endolymphatic sac tumors can be detected on MRI or CT.
- Localization of pheochromocytomas requires use of 2 imaging modalities.
  - MRI or CT coupled with iobenguane or octreotide scintigraphy, PET, or dopamine and deoxyglucose scans

A-T

- Imaging is limited.
- Cranial MRI will reveal gradual cerebellar atrophy, which is almost always noted by age 10 years.
- Imaging with radiation should be considered carefully because of these patients' extreme radiosensitivity.
  - However, is it imperative to diagnose pulmonary disease early, and chest radiographs deliver relatively little radiation compared with other modalities.
- Adult female patients and carriers should be screened for breast cancer with regular examinations and ultrasound.
  - Do not use mammograms.

DIAGNOSTIC PROCEDURES

- TSC
  - Should include an electrocardiogram
    - Especially in infants or children with evidence of cardiac rhabdomyomas
- SWS
  - Evaluation of seizures should include electroencephalography.
    - Typical findings include
      - Asymmetry, with background slowing and reduced voltage in the affected hemisphere.
      - Asymmetry becomes more prominent with the progressive cerebral atrophy.

TREATMENT APPROACH

NF1

- Management should focus on the many organ systems involved, given the wide variability of expression.
- Genetic counseling should be provided for all NF1 families.
  - Affected individuals have a 50% chance of transmission with each pregnancy.
- Careful attention should also be paid to the long bones of the lower leg.
  - Congenital tibial dysplasia is an early finding in up to 5% of children with NF1.
  - Any curvature or nodularity of the tibia is worrisome, as is any length discrepancy.
- Head circumference should be monitored at each visit.
  - ~50% of children with NF1 have macrocephaly.
- Thorough developmental evaluation should be undertaken at each visit and repeated at regular intervals, with attention to the following abilities in toddlers and preschool-age children:
  - Language
  - Visual motor skills
  - Learning
- Examination of the back for evidence of scoliosis should start by age 2 years.
  - Scoliosis appears at an earlier age in NF1.
  - Severe dystrophic form of kyphoscoliosis can appear between 3 and 5 years of age.
- Regular blood pressure assessment should begin by age 2 years.
- Ophthalmologic evaluation should be obtained annually to age 10 years.
  - Assess for the presence of optic pathway glioma.
  - Grade 1 pilocytic astrocytomas.
    - Present in ~15% of children with NF1 <10 years
    - May produce proptosis, strabismus, papilledema, or vision loss
  - If the optic chiasm is involved, hypothalamic extension can produce an endocrinopathy.
    - Results in precocious or delayed puberty.
    - Development of precocious puberty should prompt evaluation for an optic glioma.
    - Any rapid increase in linear growth should prompt an investigation for optic pathway glioma with growth hormone excess.
  - Other ocular findings may include
    - Congenital ptosis
    - Orbital asymmetry (result of sphenoid wing dysplasia)
- School-aged children should be assessed for
  - Limb asymmetry
  - Long bone bowing
  - Scoliosis
  - Cutaneous neurofibromas
- School performance should be addressed, with particular attention to
  - Learning disabilities
  - ADHD

- Executive dysfunction
- Self-esteem
- Socialization

- Teens should be assessed for
  - Limb asymmetry
  - Scoliosis
  - Neurofibromas
  - Hypertension
  - Iris hamartomas (Lisch nodules)
    - Tan to brown papules that usually appear in the teen years
    - Found in slit-lamp ophthalmologic evaluation
    - Have minimal effect other than support of diagnosis
  - Complaint of pain
    - Particularly pain associated with focal neurologic deficit or arising from a plexiform tumor
    - Should be thoroughly evaluated by examination and imaging studies
  - School performance
  - Socialization
  - Self-esteem

NF2

- Most important aspect is early diagnosis so surgery to preserve hearing can be performed.
- Advanced tumors may prevent the preservation of hearing.
  - May lead to complete deafness
  - Creates need for cochlear or auditory brain stem implants
    - Cochlear implants seem to be better than auditory brain stem implants.
- Once a diagnosis is made, the child should be evaluated by
  - Ophthalmology
  - Otolaryngology
  - Audiology
  - Imaging

TSC

- 2 basic principles.
  - Establishing correct diagnosis
  - Long-term follow-up for later manifestations
- Genetic counseling is mandatory for families and patients.
  - Disorder has autosomal-dominant inheritance.
    - Affected individuals have a 50% risk of affected offspring.
  - Germline mutations occur in ~2% of patients.
    - Seemingly unaffected parents with a single affected child have ~2% risk of having another affected child.
- Older children should be screened for
  - Seizure disorder
  - Developmental delay
  - ASD

SWS

- Seizure control is the most important aspect of management.

VHL

- Once a diagnosis is established, tumor screening and regular imaging and ophthalmologic examinations are indicated.
  - First-degree relatives should be screened for tumors.
- Annual eye examinations, including dilated funduscopy, should begin by age 6 years.
- Annual cranial and spinal MRI should begin by age 10–11 years.
- Abdominal imaging for kidneys and possible pheochromocytoma should begin by age 15–18 years.
  - May consist of ultrasound, CT, or MRI.
  - MRI is best modality for finding all the possible intra-abdominal tumors.
- Hearing loss or tinnitus should be evaluated.
  - By MRI with thin sections through the ear structures
  - By formal audiologic examination

A-T

- Most important aspects of therapy include
  - Family and patient counseling
  - Support
  - Rehabilitation
  - Assistance with the progressive ataxia

SPECIFIC TREATMENTS

NF1

- Neurofibromas present unique management issues.
  - Smaller lesions may become painful or may interfere with activities as a result of location.
  - Plexiform lesions can be disfiguring.
  - Numerous or large lesions may exert a profound effect on self-esteem and socialization.
  - Surgical excision may be necessary for problematic tumors.
- Sudden development of pain or focal neurologic deficit in plexiform tumors may represent malignant degeneration.
- Malignant peripheral nerve sheath tumors (formerly called *neurofibrosarcoma*) develop in 5%–13% of patients, with devastating effect.

- Typically arise in the 20s and 30s
- Often multicentric
- Metastasize quickly
- Usually fatal within a year

- Other malignant tumors are seen with an overall incidence 3% higher than the general population, including
  - Leukemia, especially juvenile myelomonocytic leukemia
  - Rhabdomyosarcoma
  - Pheochromocytoma (predominately adult onset)
  - Gastrointestinal stromal tumors (predominately adult onset)
  - Carcinoid (predominately adult onset)

NF2

- Management of the tumors is still primarily surgical.
  - Radiation therapy should be avoided, particularly in children, because of the risk for inducing or accelerating tumor growth.
- Screening examinations, audiometry, and imaging should be repeated at least annually starting at age 7 years.
- Children of a parent with NF2 should have
  - Annual ophthalmologic examinations starting in infancy
  - Neurologic and audiometric examinations annually from 7 years of age
- Most patients should be encouraged to learn sign language as preparation for possible future complete hearing loss.
- Patients with vestibular tumors should be counseled that problems with balance and underwater disorientation pose drowning risk.

TSC

- Treatment of epilepsy in TSC is the same as in other forms of epilepsy, with one exception.
  - Infantile spasms in TSC do not respond as well to adrenocorticotropic hormone as infantile spasms without TSC.
  - Irreversible γ-aminobutyric acid transaminase inhibitor vigabatrin is much more effective.
    - Response rates ≤96% in infants with TSC and infantile spasms.
    - Vigabatrin was approved by the US Food and Drug Administration in 2009 for treatment of infantile spasms, but concerns remain about potential severe ophthalmic toxicity.
    - Vigabatrin may be considered despite its toxicity because of potentially devastating cognitive effect of uncontrolled infantile spasms.

SWS

- Seizure control.
  - Prophylactic anticonvulsant therapy may be useful for infants with extensive intracranial disease.
  - Carbamazepine and oxcarbazepine are useful first-line anticonvulsants for SWS.
  - Other options include
    - Valproic acid
    - Topiramate
    - Phenobarbital
    - Phenytoin
    - Vigabatrin
  - Refractory seizures in SWS may lead to consideration of seizure surgery.
    - Hemispherectomy and focal resection have been found to reduce refractory seizures and improve developmental outcomes.
- Iron deficiency anemia should be corrected.
- Low-dose aspirin is suggested for prevention of stroke-like episodes.
- Prevent headaches through avoidance of
  - Fatigue
  - Sleep deprivation
  - Stress
  - Minor head trauma
- Glaucoma may be managed medically in most patients with
  - β-Adrenergic blockers
  - Carbonic anhydrase inhibitors
- Surgical approaches are not usually required.
- PWSs may be treated effectively with pulsed dye laser.

VHL

- Surgical excision generally is considered the best treatment for most symptomatic VHL tumors.
- CNS hemangioblastomas that remain stable and asymptomatic may be followed by serial imaging.
- Proper management for asymptomatic but radiologically progressive lesions is a matter of debate.
- Spinal hemangioblastomas and large or symptomatic intracranial tumors usually are resected.
- Small retinal lesions are often treated with laser photocoagulation.
  - Larger lesions may require
    - Cryotherapy
    - Brachytherapy
    - Vitreoretinal surgery
- Screening for eye lesions is of critical importance.
- Small renal tumors (<3 cm) are often followed by serial imaging.

- Larger lesions may be addressed by partial nephrectomy.
- Radical nephrectomy is rarely indicated.
- Pancreatic tumors >3 cm are generally resected.
- Almost all metastatic pancreatic tumors have ≥2 of the following features:
  - Size >3 cm
  - Mutations in exon 3 of the *VHL* gene
  - Tumor doubling time <500 days

- Symptomatic pheochromocytomas require excision.
- Laparoscopic removal of adrenal and extra-adrenal tumors is favored because of lower complication rates.

A-T

- Speech, physical, and occupational therapy should be obtained early.
  - Speech therapy may help with
    - Communication
    - Swallowing difficulties
  - Physical and occupational therapy can help with
    - Mobility
    - Safety
    - Daily living skills
- Careful monitoring is crucial for the recurrent infection and cancer risks.
- Recurrent sinopulmonary infections should be treated aggressively.
  - Aspiration should be anticipated.
- Emotional support is crucial for
  - Depression
  - Anger
  - Isolation

WHEN TO ADMIT

- NF
  - Sudden neurologic decline
  - Uncontrollable seizures
- TSC
  - Sudden neurologic deterioration
  - Intractable seizures
  - Gross hematuria
  - Heart failure or dysrhythmia
- SWS
  - Refractory seizures
- VHL
  - Hypertensive crisis with pheochromocytoma
  - Sudden neurologic deterioration
- A-T
  - Severe pulmonary infection, especially if respiratory distress is present
  - Severe aspiration event

WHEN TO REFER

- NF1
  - Pediatric ophthalmologic evaluation beginning in the first year
  - Neurologic evaluation if seizures are difficult to manage
  - Neurodevelopmental testing if evidence of
    - Learning disability
    - ADHD
    - Speech delay
  - Surgical referral for symptomatic neurofibromas, renovascular hypertension
- NF2
  - Hearing loss
  - Tinnitus
  - Gait or balance difficulty
  - Headache
- TSC
  - Ophthalmologic screening
    - In infancy if TSC is suspected
  - Neurologic screening
    - When seizures are hard to manage or progressive
  - Surgery
    - Symptomatic or progressive renal lesions >4 cm
  - Neurodevelopmental testing
    - At diagnosis, and periodically
- SWS
  - Ophthalmologic evaluation
    - Any infant with forehead and eyelid PWS
  - Neurologic evaluation
    - Difficult seizure management
- VHL
  - Ophthalmologic examination
    - By age 6 years or with any sudden vision change
  - Neurologic examination or neurosurgery
    - On detection of CNS tumors
  - General surgery
    - On detection of intra-abdominal tumors
  - Audiology
    - At diagnosis or onset of auditory symptoms
- A-T
  - Neurologic examination
    - On development of ataxia
  - Speech therapy
    - On development of speech or swallowing difficulty
  - Physical and occupational therapy
    - Before ataxia becomes severe

FOLLOW-UP

TSC

- Neurobehavioral assessment and monitoring
  - Routine formal testing should be performed at age-appropriate levels in
    - Infancy
    - Preschool
    - Early school age
    - Periodically into adulthood
  - Identify cognitive and behavioral issues as early as possible.
  - Any developmental or behavioral regression or new cognitive dysfunction should prompt urgent reevaluation.
- Brain and abdominal imaging should be performed at least every 3 years.
  - More often if lesions exhibit progressive growth or if any acute change in symptoms occurs.
    - Sudden neurologic or cognitive decline
    - Hypertension
    - Hematuria
  - Annual brain MRI is suggested at age 21 years.
  - Annual renal imaging is suggested for monitoring of angiomyolipomas.
  - Serial renal ultrasound is adequate if maximal lesion size is <4 cm.
  - Larger renal lesions should be assessed by Doppler, MRI, or magnetic resonance angiography for abnormal vasculature.
  - Chest CT is indicated for all women with TSC to evaluate for possible lymphangiomyomatosis.
  - Women with lung lesions should have annual pulmonary function tests.

VHL

- Lifelong surveillance is required, even after excision of tumors, because of late-onset presentation of new tumors and the risk for late tumor recurrences.

COMPLICATIONS

NF1

- Optic pathway gliomas develop in 15%–20% of patients at a mean age of 4.2 years.
  - Annual ophthalmologic monitoring from the first year of life and continue to age 10 years, checking for
    - Vision change
    - Afferent pupillary defect
    - Change in funduscopic examination findings
  - Other ocular findings may include
    - Congenital ptosis
    - Congenital glaucoma
    - Pulsating exophthalmos
  - If optic pathway glioma is present, MRI evaluation should be repeated every 2 years until age 10 in addition to annual ophthalmologic examination.
  - Precocious or delayed puberty may be a later clinical sign of optic glioma extending from the chiasm into the hypothalamus and should prompt re-evaluation and MRI.
- Hormonal surges.
  - Should be discussed with preteens and teens
  - Factors likely to cause increases in both size and number of neurofibromas
    - Oral contraceptives
    - Puberty
    - Pregnancy
- Neurologic and neurodevelopment issues.
  - Headaches occur in 20% of patients.
    - Usually migraines that respond well to standard therapy, such as amitriptyline or topiramate
  - Seizures occur in 4%–10%.
    - Management should be directed toward the specific seizure type.
  - Hearing loss, usually unilateral, occurs in ~10% of patients.
  - Various learning disabilities are observed in 35%–65% of children.
    - Math and reading comprehension problems.
    - Visual perception deficits.
    - Delays in gross- and fine-motor skills.
    - Speech and language delays in ~50%.
    - ADHD is common, occurring in ~50%.
    - ASD in ≤14%.
  - Various behavioral problems, often in association with a comorbid diagnosis of ADHD.
    - Anxiety
    - Depression
    - Social problems
    - Aggression
    - Unusual behaviors
- Vascular disease is more common and may include
  - Congenital heart defects
  - Hypertension
  - Occlusive arterial disease
  - Aneurysms
  - Arteriovenous fistulas

- Hypertension.
  - In young children as a result of renal artery stenosis in 1% of patients
  - In adults as primary hypertension or associated with pheochromocytoma
  - Workup should include
    - Renal angiography in children
    - Urine catecholamine levels in adults
- Bone abnormalities
  - Range from skeletal dysplasia to non-ossifying fibroma to short stature to kyphoscoliosis.
  - Long bone dysplasia (especially tibial) may be seen during the first year of life.
    - May present as bowing or, rarely, pseudo-arthrosis (nodule at the site of a healing pathological fracture).
    - Pseudoarthrosis occurs in only 3%.
  - Non-ossifying fibromas occur in late childhood to the teen years.
    - May lead to pathological fractures, particularly in the femur, tibia, and humerus
  - Scoliosis is seen in 10%.
    - May develop earlier than in the general population
  - Aggressive dystrophic form may develop between 3 and 7 years of age.

TSC

- Heart failure in infancy
- Hypertension secondary to
  - Renal cystic disease
  - Adrenocorticotropic hormone used to control infantile spasms
- Nephrolithiasis secondary to
  - Renal cystic disease
  - Ketogenic diet
  - Drugs such as topiramate
- Various dysrhythmias
  - Wolff-Parkinson-White syndrome
- RCC
  - Less common but potentially severe complication
  - Lifetime risk is the same in TSC as in the general population
  - Average age of onset is 28 years in TSC versus 52 years in the general population.
  - Overall morbidity of renal lesions is predominantly related to angiomyolipomas.
- Symptomatic lymphangiomyomatosis
  - Often progressive
  - Leading cause of death among women with TSC

SWS

- Some patients may develop sudden stroke-like episodes of weakness, even in the absence of seizures.
  - May be transient
  - May leave permanent hemiplegia
- Hemianopsia may develop in up to 50% of patients.

VHL

- Major causes of death are
  - RCC
  - Complications from CNS hemangioblastomas

A-T

- Patients with A-T are at higher risk (one-third) for developing cancer.
  - In children, acute lymphoblastic leukemia predominates.
  - Other lymphoid tumors include
    - B-cell non-Hodgkin lymphoma
    - T-cell lymphoma
    - Hodgkin disease
  - Older children sometimes develop
    - T-prolymphocytic leukemia
  - Adults tend toward nonlymphoid cancers such as
    - Breast
    - Stomach
    - Ovarian
    - Liver
    - Uterus
    - Melanoma
    - Basal cell skin cancer
  - Women who are *ATM* mutation carriers have a 5-fold increase in risk of breast cancer compared with the normal population.
  - ~15% of patients with A-T die of lymphoid malignancies during childhood.
- Patients with A-T are susceptible to injury by ionizing radiation and radiomimetic chemotherapeutic drugs.
  - Because of the inability to repair defective DNA, this susceptibility complicates therapy for the various malignancies.
  - Exposure to these agents poses life-threatening risk to patients with A-T.

PROGNOSIS

NF1

- Life expectancy is ~10–15 years shorter compared with the general population.
- Malignancy and vascular disease are the leading causes of death.

NF2

- Prognosis is poor despite the benign nature of the tumors.
- Location of the tumors often increases morbidity and mortality, with average age at death of 36 years.
  - Survival for patients presenting at age 30 in the past 20–30 years was 15 years from diagnosis.
- Early detection and removal of tumors shows promise for prolonged survival.

TSC

- Determination of the type of mutation is important for prognosis and may allow more selective emphasis on specific management strategy by mutation type.
- Large numbers of tubers are associated with worse overall prognosis.
  - Infantile spasms
  - Cognitive impairment
  - Difficult seizure control
- Presence and number of subependymal nodules do not seem to correlate with severity of neurologic symptoms.
- With any type of seizures, better control seems to improve prognosis.
  - Seizures become refractory to treatment in ≤50% of children with TSC.

SWS

- Earlier onset may predict worse outcome.
  - Poor seizure prognosis
  - More difficult seizure control
  - Higher risk of cognitive impairment (somewhat controversial)
- Bilateral leptomeningeal angiomatosis (7%–26% of patients) has poor neurologic prognosis.

VHL

- Visual prognosis is better when ocular lesions are detected before development of symptoms.
- Metastatic RCC is a leading cause of death in patients with VHL.

A-T

- Life expectancy varies.
- Survival into the sixth decade is likely.
- Leading causes of death are
  - Malignancy
  - Infection
  - Pulmonary failure
    - — From combined recurrent infection and recurrent aspiration

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DEFINITION

- A variety of paroxysmal nonepileptic disorders occurring in children with a wide range of clinical features that mimic seizures.
- Distinguishing these from seizures is important so that the child is not treated inappropriately with anticonvulsants.
  - Syncope (fainting) is an acute and transient loss of consciousness caused by reduced cerebral perfusion.
  - Benign paroxysmal vertigo is a disorder characterized by brief attacks of vertigo.
  - Shuddering attacks or shivering episodes are a benign movement disorder.
  - Sleep-related myoclonus in neonates is called *benign neonatal sleep myoclonus*.
  - Night terrors or sleep terrors are a sleep disorder with some features that mimic partial complex seizures.
  - Narcolepsy is a sleep-wake disorder characterized by excessive and inappropriate periods of sleep during the day.

HISTORY

- A thorough history is often all that is needed to make the diagnosis.
  - A few patients may require more extensive evaluation.
- Breath-holding spells.
  - The most important features of the evaluation are
    - History of the episode.
    - Surrounding events.
    - Familial incidence of breath-holding spells is high; parents should be questioned about episodes in other family members.
- Syncope.
  - Obtain a description of the event by the patient and an observer.
- Night terrors.
  - Affected children often have a family history of night terrors or another sleep disorder.

DIFFERENTIAL DIAGNOSIS

- Breath-holding spells can be divided into 2 types: cyanotic and pallid.
  - Cyanotic
    - Usually precipitated by frustration or anger.
    - During spells, children cry vigorously and then hold their breath in expiration.
    - Apnea is followed by cyanosis, with opisthotonic posturing and loss of consciousness.
    - Recovery is usually quick, with return of respiration and consciousness in <1 minute.
  - Pallid
    - Usually provoked by sudden fright or minor injuries, especially falling and hitting the occiput.
    - The child gasps or cries briefly and then abruptly becomes quiet.
      - The child loses consciousness, has pallor, and becomes limp.
      - The child may develop clonic jerks.
- Syncope.
  - Patients have presyncopal symptoms that may include
    - Light-headedness.
    - Anxiety.
    - Sweating.
    - Nausea.
    - Generalized numbness.
    - Visual changes described as constriction or darkening of vision.
    - Observers notice marked pallor and clammy skin.
  - Presyncopal symptoms are followed by loss of consciousness and slumping to the floor.
    - Once the patient is recumbent and cerebral perfusion is restored, consciousness returns within a few seconds.
    - If patient is held with the head above the body and cerebral perfusion is not restored, clonic movements may occur.
    - Patients may be tired but are not disoriented or confused after an episode of syncope.
- Benign paroxysmal vertigo.
  - Characterized by abrupt onset.
    - The child appears fearful and cannot maintain normal posture and gait.
    - The child may seek support and clutch the parent, and then abruptly sit down or fall.
    - In severe cases, the child may be limp and incapable of using the extremities.
    - Pallor and diaphoresis are usually apparent.
    - Vomiting and nystagmus sometimes occur.
  - An episode typically lasts <30 seconds.
    - May last a few minutes in rare cases.
    - A brief period of postural instability may follow, which usually resolves within a few minutes.
    - Consciousness is not altered during the episode.
    - The child rarely feels sleepy afterwards.

- History and physical examination usually differentiate from
  - — Brain stem lesions
  - — Posterior fossa tumors
  - — Epilepsy

■ Shuddering attacks.
- Episodes are brief.
- Characterized by paroxysmal rapid tremors involving, primarily, the head and arms.
  - — Some episodes may involve flexion of the head, elbow, trunk, and knees, with adduction of the elbows and knees.
- Consciousness is not altered during the episodes.
- Emotional factors, including excitement, fear, anger, and frustration, may precipitate episodes.
- Not epileptiform in nature.

■ Benign neonatal sleep myoclonus.
- Myoclonus presents only during quiet sleep and disappears when the infant awakens.
- Jerks occur every 2–3 seconds for several minutes and have been reported to last ≤12 hours.
- Jerking movements may begin bilaterally or start in one extremity and then progress to involve the other extremities.
- Rocking the crib and repetitive sounds may provoke the myoclonus.
- Differentiated from seizure disorder by
  - — History of episodes during sleep only
  - — Normal electroencephalogram

■ Night terrors.
- Episodes usually occur during the first 2 hours after falling asleep.
- Child sits up in bed abruptly and screams or talks unintelligibly.
- If the child's eyes are open, they have a glazed look.
- During the episode, the child appears to be hallucinating and does not respond to parents.
- Response of the sympathetic nervous system includes tachycardia and diaphoresis.
- In some cases, the child may sleepwalk.
- Episode usually lasts 10 minutes; the child then relaxes and abruptly falls back to sleep.
- On awakening, the child does not remember the episode.
- Nightmares should be differentiated from night terrors.
  - — Nightmares occur during rapid eye movement sleep.
  - — Nightmares are associated with easy arousal and recall of the content, or at least the occurrence of the nightmare.

■ Narcolepsy.
- Interrupts activities.
- Does not diminish in response to adequate amounts of sleep at night.
- Naps may last from a few minutes to >1 hour.
- Included in the differential diagnosis of excessive daytime sleepiness are chronic illness, sleep apnea, hypothyroidism, depression, and seizures.

LABORATORY EVALUATION

■ Laboratory evaluation is seldom needed for any of these disorders.

■ Narcolepsy.
- A strong association exists between narcolepsy and the human leukocyte class II antigen DQB1*06:02.
- Human leukocyte antigen typing may be helpful but is not diagnostic.
- The hypocretin peptides that are important for maintaining wakefulness may be absent on cerebrospinal fluid studies.

DIAGNOSTIC PROCEDURES

■ Syncope
- If atypical features are present, electroencephalography or a cardiac evaluation, including Holter monitoring, may be appropriate.
  - — Absence of a precipitating factor
  - — Confusion after the episode
- Evaluation with tilt table testing can be helpful for children who have unexplained syncope.

■ Benign paroxysmal vertigo
- Oculovestibular testing with cold-water calorics
  - — Difficult to perform in young children.
  - — Results vary, but when properly done, testing shows no abnormalities in vestibular function.
- Radiographic studies of the temporal bone and electroencephalographic recordings
  - — Results are within reference range.

■ Benign neonatal sleep myoclonus
- Electroencephalographic results are typical, with no epileptiform discharges associated with the myoclonus.

■ Narcolepsy
- Sleep studies are important in diagnosing narcolepsy.

TREATMENT APPROACH

- In general, the approach with most nonconvulsive periodic disorders is to
  - Educate the parents about the disorder.
  - Reassure parents that the disorder will not lead to intellectual disability or epilepsy.
  - Explain that most of the disorders are time-limited and will resolve on their own.
- Narcolepsy is the exception.
  - It is a lifelong disorder that must be accurately diagnosed and subsequently treated.

SPECIFIC TREATMENT

Breath-Holding Spells

- Treatment is directed mainly at reassuring the family of the benign nature of the episodes.
- Emphasize that the episodes are not seizures and do not lead to intellectual disability or epilepsy.
- Anticonvulsants should not be used.
  - They are not effective in treating cyanotic or pallid breath-holding spells.
- Cyanotic episodes.
  - Often precipitated by temper tantrums, anger, and frustration.
  - Advice about behavior management may be helpful.
- Pallid breath-holding spells.
  - Anemia has been described as a contributing factor.
  - Treating anemia may reduce the incidence of the episodes.
  - Atropine is effective for pallid breath-holding episodes; however, its use is rarely warranted.

Syncope

- Teach the patient and family about managing an episode.
- When patients have presyncopal symptoms
  - They should sit or lie down as soon as symptoms begin to prevent progression to loss of consciousness.
  - If the child loses consciousness, place him in a recumbent position, with the head lower than the trunk.
  - Parents should be cautioned against picking up a child who has fainted, as this may prolong the period of unconsciousness.

Benign Paroxysmal Vertigo

- In most cases, no treatment is necessary.
- Anticonvulsants are not effective.
- Antihistamines have been used in some patients who have frequent episodes.
  - Some have noted apparent reduction in the number of episodes.
  - Assessing the effect of therapy accurately is difficult because frequency of attacks varies.

Shuddering Attacks

- In most cases, no treatment is necessary.
- If episodes are severe and interfere with activities, treatment with propranolol may be helpful.
- Anticonvulsants are ineffective and should not be used.

Benign Neonatal Sleep Myoclonus

- No treatment is necessary.
- Reassure parents that these neonates do not subsequently develop epilepsy or cognitive delay.

Night Terrors

- The nature of the episodes should be explained to parents.
- Parents tend to try to wake and reassure the child.
  - Attempts to awaken the child are not helpful and may increase agitation.
- Parents should be told that the child is not aware of their presence.
- If the child is sleep deprived as a result of night terrors, parents should take steps to increase the amount of sleep the child is getting.
- If night terrors persist despite adequate sleep
  - A sleep study may be needed to evaluate for obstructive sleep apnea, which can trigger night terrors.
- In most cases, no medication is indicated.
  - If episodes are frequent or severe, medications may be helpful.
    - Benzodiazepines
    - Imipramine
    - L-5-Hydroxytryptophan

Narcolepsy

- Central nervous system stimulants help reduce the frequency of naps.
  - Methylphenidate
  - Modafinil
- Tricyclic medications are used to treat cataplexy and the other associated symptoms.
  - Imipramine

WHEN TO REFER

- If a diagnosis cannot be made by history and physical examination
- If a need exists for subspecialty expertise

WHEN TO ADMIT

- Admission may be necessary if the child needs video electroencephalographic monitoring to evaluate an episode.

COMPLICATIONS

- Narcolepsy
  - In addition to excessive daytime sleep, patients often have
    - Cataplexy, a transient partial or complete loss of tone
      - Often triggered by an emotional reaction (eg, laughter, fright).
    - The individual does not lose consciousness.
    - Sleep paralysis
      - Occurs as the patient falls asleep or awakens
      - Characterized by the inability to move or speak
    - Hypnagogic hallucinations
      - Occur while falling asleep
      - Can be auditory or visual
      - May be very frightening to a child

PROGNOSIS

- Breath-holding spells (cyanotic or pallid) have an excellent prognosis.
  - Most children outgrow such episodes by school age.
- Benign paroxysmal vertigo attacks usually stop spontaneously over a few years.
  - Some children may later develop migraine headaches.
- Shuddering attacks.
  - The number of episodes usually declines gradually.
- Benign neonatal sleep myoclonus usually diminishes gradually during the first 6 months of life.
  - Rarely lasts >3 years
- Narcolepsy is a lifelong condition that needs to be monitored and treated.

DEFINITION

- Definitions of *overweight* and *obesity* are based on body mass index (BMI).
  - BMI = weight in kilograms divided by height in meters squared
    - Approximates a person's body fat.
    - Correlates well with medical complications associated with obesity.
    - Easily calculated from standard measurements obtained during health supervision visits.
    - In children, body fat changes throughout development, so BMI percentile must be used.
- For children and adolescents.
  - Overweight: BMI between the 85th and 95th percentiles for age and sex
  - Obese: BMI ≥95th percentile
- Metabolic syndrome (syndrome X).
  - Cluster of metabolic abnormalities that leads to cardiovascular disease and increased risk of mortality

SIGNS AND SYMPTOMS

- Clinical manifestations of metabolic syndrome
  - Obesity
    - Excess body fat
    - Increased visceral fat
    - Central fat distribution
  - Insulin resistance
  - Dyslipidemia or hypertriglyceridemia
  - Hypertension
  - Glucose intolerance or non–insulin-dependent diabetes mellitus

DIFFERENTIAL DIAGNOSIS

- Primary medical causes of obesity are rare.
- Endocrine and genetic causes of obesity often cause short stature or cognitive impairment.
  - Hypothyroidism
    - Associated with short stature
    - Weight gain, fatigue, constipation, cold intolerance, myxedema
    - Testing: thyroid-stimulating hormone, free thyroxine
  - Cushing syndrome
    - Short stature
    - Central obesity, hirsutism, moon facies, plethora, hypertension
    - Testing: dexamethasone suppression test
  - Pseudohypoparathyroidism
    - Short stature
    - Short metacarpals, subcutaneous calcifications, dysmorphic facies, intellectual disability, hypocalcemia, hyperphosphatemia
    - Testing: urinary cyclic adenosine monophosphate after synthetic parathyroid hormone infusion
  - Growth hormone deficiency
    - Short stature
    - Fatigue
    - Testing: evoked growth response, insulin-like growth factor 1
  - Down syndrome
    - Short stature
    - Dysmorphic facies, intellectual disability
    - Testing: karyotyping
  - Turner syndrome
    - Short stature, web neck
    - Testing: karyotyping
  - Prader-Willi syndrome
    - Cognitive impairment
    - Hypogonadism, small hands and feet
    - Testing: fluorescence in situ hybridization *15q11* microdeletion (70% of cases)
  - Bardet-Biedl syndrome
    - Cognitive impairment
    - Retinitis pigmentosa, renal abnormalities, polydactyly, hypogonadism
    - Testing: *BBS1* gene
  - Biemond syndrome
    - Cognitive impairment
    - Iris coloboma, hypogonadism, polydactyly
    - Testing: clinical
  - Alström syndrome
    - Cognitive impairment
    - Retinitis pigmentosa, diabetes mellitus, hearing loss
    - Testing: *ALMS1* gene

DIAGNOSTIC APPROACH

- The Centers for Disease Control and Prevention provides age- and sex-specific growth curves for BMI.
- Electronic medical records allow routine calculation and plotting of BMI when height and weight data are entered.

LABORATORY FINDINGS

- Calculation of BMI.
- Fasting lipid screening recommended by the American Academy of Pediatrics (AAP) for
  - Children and adolescents with BMI ≥85th percentile
  - Those with family history of dyslipidemia, cigarette smokers, and those with diabetes mellitus
- The National Heart, Lung, and Blood Institute recommends universal pediatric lipid screening beginning with a non-fasting lipid screen.
- Hemoglobin A_{1c} is sometimes used to screen patients who cannot comply with fasting before laboratory testing.
- Insulin levels.
  - Not recommended for evaluating obesity
- Liver function tests.
  - At baseline
  - Before pharmacologic management for type 2 diabetes
  - Before surgical intervention for obesity
- Indications for diabetes testing (fasting blood glucose) include[1]
  - Patient is obese, with BMI >95th percentile.
  - Patient is overweight (BMI >85th percentile for age and sex), and any 2 risk factors.
    - Family history of type 2 diabetes in a first- or second-degree relative
    - Native American, African American, Latino, Asian American, and Pacific Islander
    - Signs of insulin resistance or associated conditions
      - Acanthosis nigricans
      - Hypertension
      - Dyslipidemia
      - Polycystic ovary syndrome
      - Small for gestational age
    - Maternal history of diabetes or gestational diabetes
  - Age to initiate screening
    - 10 years, *or*
    - Onset of puberty if <10 years
  - Frequency: every 3 years
  - Preferred screening test: plasma glucose after an 8-hour fast
- **Table 1** lists other tests.
- Metabolic syndrome.
  - Insulin resistance (decreased B-cell count)
    - Elevated fasting insulin levels
    - Fasting insulin level >15 mg/dL
    - Peak insulin level >150 mg/dL
  - Dyslipidemia or hypertriglyceridemia
    - Low high-density lipoprotein cholesterol
    - Increased free fatty acids
  - Glucose intolerance or non–insulin-dependent diabetes mellitus
    - Fasting plasma glucose level >126 mg/dL
    - 2-hour plasma glucose level >200 mg/dL (oral glucose tolerance test)

IMAGING

- See **Table 1.**

TREATMENT APPROACH

- Preventing secondary comorbidity and disability is the principal goal in treating overweight children and adolescents.
- Obesity should be approached as a chronic condition that requires permanent lifestyle changes to achieve optimal body weight.
- Prescribing a treatment plan without engaging the child and family can lead to frustration, impairing future attempts at weight control.
- Enhancing the therapeutic relationship can begin with a question to the parent.
  - "Have you ever struggled with your weight?"
    - The answer reveals the family's perception of body weight as an indicator of health and well-being and the parent's empathy for their child.
- Readiness to change can be assessed by asking the child and parent 3 questions.
  - "How concerned are you about your (your child's) weight?"
  - "Do you think that you can improve your (your child's) body fitness?"
  - "Do you think that your family can change eating and physical activity patterns?"
- Once the patient and family are ready to begin a treatment plan, the clinician should assist in setting realistic goals.
- Weight maintenance rather than weight loss is usually the first step.
  - The objective is to decrease the rate of weight gain and allow the child to achieve healthier body mass.
  - Learning healthy eating and activity habits improves health over time.
  - Focusing on health and healthy behavior changes allows gradual and long-term change.
  - Fad diets and very low-calorie regimens are not recommended because they cannot be maintained.

Table 1. Laboratory Testing as Indicated by Screening Guidelines, History, or Physical Examination

Test	Indications
Thyroid function tests	When symptoms of hypothyroidism are present
Plain-film radiographs	For deformity, hip or knee pain (SCFE or Blount disease [tibia vara])
Head CT scan, lumbar puncture	Headache, visual changes, papilledema (pseudotumor cerebri)
LH, FSH, total and free testosterone; consider pelvic ultrasound.	Menstrual irregularity, acne, hirsutism (PCOS)
Genetic consultation, karyotype	Short stature, dysmorphic features, cognitive impairment
Lipid panel	2–8 y if family history of dyslipidemia or early cardiovascular disease (<55 y in males, <65 y in females) or if child has diabetes, hypertension, BMI >95th percentile, smokes cigarettes, or has moderate- to high-risk medical condition (ie, renal failure, hypothyroidism, and liver failure) 9–11 y: universal screening for all children[a] 17–21 y: universal screening for all children/young adults

Abbreviations: BMI, body mass index; CT, computed tomography; FSH, follicle-stimulating hormone; LH, luteinizing hormone; PCOS, polycystic ovary syndrome; SCFE, slipped capital femoral epiphysis.

[a] Current recommendation at the time of publication.

  - Children with acute comorbid conditions, such as sleep apnea, may be managed medically on a very low-calorie diet, usually in an inpatient treatment program.
- Recommendations for weight maintenance or weight loss are based on
  - Level of overweight or BMI.
  - Age.
  - Existence of complications.
  - Setting goals for weight maintenance or weight loss may be based on BMI, age, and complications.
- Role of pediatrician.
  - Intervene early.
  - Assess the family's readiness to change.
  - Educate the family about medical complications of obesity.
  - Involve the family and caregivers in the treatment program.
  - Aim for permanent dietary and activity change.
  - Avoid short-term diets or exercise programs aimed at rapid weight loss.
  - Teach the family to monitor eating and activity.
  - Assist the family in making small, gradual changes.
  - Encourage and empathize.
  - Avoid criticism.

SPECIFIC TREATMENTS

Pharmacologic Approach

- Weight loss
  - No evidence exists that pharmacologic agents for weight loss are safe and effective for children.
- Hyperlipidemia
  - Lipid-lowering medication is considered if behavioral modifications are unsuccessful.
- Metabolic syndrome
  - Evidence for short- and long-term efficacy of pharmacologic treatment of metabolic syndrome in youth remains sparse.
    - Studies of oral hypoglycemics (specifically metformin) in adolescents have demonstrated reductions in blood glucose but have shown little effect on insulin resistance or lipid abnormalities.

Counseling

- May be necessary for the family of a child who is seriously obese (>99th percentile) or has medical complications.

Bariatric Surgery

- May be considered in severely obese adolescents (BMI >40) with all of the following conditions:
  - Nearly complete skeletal maturity
  - Significant medical complications
  - Inability to change weight- or obesity-related comorbid conditions despite dietary and exercise modifications for 6 months
- After evaluation by a multidisciplinary team, surgery can be performed by surgeons experienced in gastric bypass.
- The major challenge is how to give informed consent or assent about the consequences of obesity and the alternative of bariatric surgery.
  - The procedure changes the individual's ability to eat and may have unforeseen long-term consequences.
  - On the other hand, obesity may be life-threatening.

Dietary Modifications

- Drink water, sugar-free beverages, or milk with ≤1% fat.
- Use cooking spray instead of frying.
- Make cut-up fruits and vegetables accessible.
- Limit seconds to fruits and vegetables.
- Serve appropriate portions.
  - Meat: size of palm
  - Starch: ½ cup
- Review school lunch menu with the child to pick healthy options.
- Pack a lunch with 4 oz of lean meat, whole-grain bread, fruit or vegetable, and milk.
- Limit restaurant dining to once per week or less.
- Limit fast food to rarely.
- Eat meals together, and turn off the television while eating.
- Schedule at least 20 minutes for each meal.
  - Eating slowly helps to avoid overeating.
- Eat regular meals.
  - Skipping meals can lead to overeating.
- Remove snack foods, chips, cookies, and desserts from the house.
- Allow occasional treats.
- Make salads with vegetables, and not eggs, meat, bacon, or cheese.
  - Toss the family salad to decrease amount of dressing.

Recommendations for Increasing Physical Activity

- Limit television and video games to no more than 1–2 hours per day.
- Engage in active family activities (eg, biking, walking after dinner, swimming, going to zoo/museum).
- Dance to your favorite music.
- Walk with a friend rather than talking on the telephone.
- Walk while you talk on the telephone.
- Engage in team sports.
- Take classes: dance, martial arts, or swimming.
- Strategies for toddlers and preschool-aged children include
  - Engage in outdoor play every day.
  - Engage in active indoor play with soft balls, jumping, or bouncing balls.
  - Buy active toys rather than computer games or videos.
- Strength training.
  - Overweight children often find this rewarding and benefit psychologically and physically.
    - — Given their body mass, they may be stronger than peers.
    - — It does not require aerobic endurance or agility.

Parenting Skills for Weight Loss

- Find reasons to praise the child's behavior.
- Set clear guidelines about food.
- Avoid using food as a reward.
- Establish daily family mealtimes, family snack times, and physically active family time.
- Determine what food is offered and when.
- Allow child to decide whether to eat.
- Offer only healthy options.
- Remove temptations (eg, snack food in home).
- Walk instead of drive; take the stairs.
- Decrease television viewing time.
- Be a role model in diet and physical activity.
- Be consistent.

Metabolic Syndrome

- Treatment is aimed primarily at weight reduction and treating component diagnoses: hypertension, diabetes, and hyperlipidemia.
- Behavioral and dietary modifications are first-line therapy.
- Metformin may be helpful as an adjuvant therapy.

WHEN TO ADMIT

- The morbidly obese patient with a BMI >40 kg/m^2 may need to be hospitalized for a low-calorie weight-reduction program.

WHEN TO REFER

- Refer to a pediatric obesity center for acute complications, such as
  - Pseudotumor cerebri
  - Sleep apnea
  - Obesity hypoventilation syndrome
  - Orthopedic problems

FOLLOW-UP

- A key role for child health professionals is monitoring.
  - BMI should be calculated and plotted at each health supervision visit.

COMPLICATIONS

- Obesity is associated with medical comorbid conditions in many organ systems (**Table 2**).
  - Some problems are apparent after a relatively short duration of excess body fat.
  - Other complications do not arise for decades.

PROGNOSIS

- Early childhood obesity often resolves.
  - Optimism is warranted in early years.
- By adolescence, nutritional and activity patterns are more difficult to change, and families have less influence.
- Obesity remains an emotionally charged issue, creating more difficulties for the family and clinician than do more purely medical problems.
- Blood pressure can decrease with as little as 5–10 pounds of weight loss.
- The age at which the child becomes obese is related to how likely the child is to be obese in adulthood.
  - Children who are obese from 6–11 years of age
    - 50% of girls and 30% of boys will be obese as adults, compared with 18% of age-matched peers.
  - Obesity during adolescence
    - >60% will maintain obesity into adulthood.
  - Obese adults who became obese during childhood
    - More likely than those who become obese during adulthood to have severe obesity (BMI >40 kg/m^2)
- Overweight and typical-weight children with one obese parent are at twice the risk of adult obesity compared with children without an overweight parent.
  - Overweight 10- to 14-year-olds with ≥1 obese parent: 80% will remain obese as adults.

PREVENTION

- Prevention of childhood obesity.
  - Crucial to public health
  - Requires concerted effort of
    - Public health officials
    - Government at all levels
    - Schools
    - Health care system
- Clinicians should educate families about the importance of healthy nutrition and physical activity from the earliest years.
  - Healthful nutrition begins with breastfeeding.
    - Associated with lower childhood obesity risk.
    - Exclusive breastfeeding is recommended for the first 4–6 months of life.
    - Introduce infant foods no earlier than 4–6 months.
      - Provide a range of flavors, including vegetables.
  - Consideration of nutrient quality and caloric content.
    - Reserve calorie-laden foods with little nutritional value for occasional treats.
    - Plan meals and snacks based on fruits, vegetables, and grains.
    - Meat and dairy products
      - Should supply fewer calories than fruits, vegetables, and grains
    - Low-fat milk is recommended for most children >2 years.
    - Children should be encouraged to drink water to quench thirst.
      - Reserve highly sugared beverages for occasional treats.
      - Fruit juice (1 per day, <4 oz).
    - Healthy desserts include
      - Fruit
      - Yogurt
      - Cookies made with oatmeal
      - Occasional puddings made with milk and eggs
      - Ice cream
    - Using less saturated fat is suggested for cardiovascular health.
    - Attention to portion size is important.

Table 2. Medical Conditions Associated With Obesity

Condition	Disease	Description
Cardiovascular	Hypertension	SBP >95th percentile for sex, age, and height
	Dyslipidemia	LDL >130 mmol/L HDL <40 mmol/L Total cholesterol >200 mmol/L
	Cardiovascular disease	Atherosclerosis begins during childhood.
Endocrine	Type 2 diabetes mellitus	FBG >110 mg/dL
	Insulin resistance	Increased serum insulin levels
	Polycystic ovary syndrome	Menstrual irregularities, hirsutism, acne, insulin resistance, hyperandrogenism
	Metabolic syndrome	Obesity, hypertension, dyslipidemia, insulin resistance
Gastrointestinal	Nonalcoholic fatty liver disease	Increased transaminases; may progress to fibrosis or cirrhosis
	Gallbladder disease	May account for 50% of cases in adolescents
Pulmonary	Obstructive sleep apnea	Snoring, apnea, restless sleep, behavioral problems
Orthopedic	Slipped capital femoral epiphysis	Hip or knee pain, decreased mobility of hip
	Blount disease (tibia vara)	Severe bowing of the tibia
	Osteoarthritis	May present in adolescence
Neurologic	Pseudotumor cerebri	Headaches, vision changes, papilledema
Psychiatric	Anxiety	
	Low self-esteem Depression	Sometimes difficult to assess whether the depression or low self-esteem is the cause of the weight gain or if the weight gain is the cause of the depression.
Oncologic	Endometrial cancer Breast cancer Colon cancer	Increased prevalence with adult obesity

Abbreviations: FBG, fasting blood glucose; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SBP, systolic blood pressure.

- Encourage physical activity.
  - Children whose parents are physically active are more likely to be physically active.
  - Clinicians can encourage families to plan opportunities for physical activity as a parental responsibility.
  - Children should engage in ≥60 minutes of physical activity on most, preferably all, days.
  - Children who participate in organized sports should be encouraged to be physically active on days without organized activities.
    - Pediatricians can reinforce the importance of daily physical activity and to resist reliance on organized sports for all of a child's physical activity.
  - Older children and adolescents may benefit from strength training.

- Increased physical activity should be accompanied by a decrease in sedentary activities.
  - Limiting television or other recreational screen time to <2 hours per day is recommended.
  - The AAP recommends no television for children <2 years.
- Parents should strive to be role models in their dietary and physical activity habits.
  - Child health professionals can begin to talk to parents about healthy nutrition and activity during the first year of their child's life.
  - Themes can be revisited at annual health supervision visits.

■ Monitoring.

- Tracking growth trajectories and explaining patterns to parents is an essential component of primary prevention.
- Children with increasing BMI percentiles may be at risk for obesity.
  - Health care professionals can help families evaluate nutritional and activity patterns and make adjustments.

REFERENCE

1. Adapted from American Diabetes Association. Standards of medical care in diabetes—2014. *Diabetes Care.* 2014;37 (Suppl 1):S14–S80. Copyright © 2014 American Diabetes Association. Reprinted with permission

Odor (Unusual Urine and Body)

DEFINITION

- Unusual odors may be a chief complaint, symptom, or sign and provide clues in diagnosis of many specific conditions.
- Unusual odors may emanate from
  - Breath
  - Urine
  - Skin
  - Sputum
  - Vomitus
  - Stool
  - Vagina
- *Bromhidrosis* refers to malodorous and offensive sweat.
  - Caused by decomposition of products from the apocrine, eccrine, and sebaceous glands.
  - Apocrine bromhidrosis begins after puberty with a characteristic acrid or sweaty odor.
  - Eccrine bromhidrosis results from bacterial interaction with moist keratin.
    - Associated with hyperhidrosis, obesity, intertrigo, and diabetes mellitus
    - Aggravated by hot weather and occurs primarily in the soles, palms, and intertriginous areas
- *Halitosis* is offensive odor emanating from the mouth or air-filled cavities (nose, sinuses, or pharynx).
  - May be physiologic or pathologic.
  - Causes include xerostomia (dry mouth), periodontitis, sinusitis, tonsillitis, or gastroesophageal reflux.

HISTORY

- When approaching the differential diagnosis of unusual odors, first conduct a thorough history and physical examination.
- If unusual body odor is the chief symptom, a history of present illness helps.
  - Questions may include
    - When did you first notice the odor?
    - What does it smell like?
    - Does it smell like anything familiar?
    - What is the quality?
    - What is the intensity?
    - Does it seem to come from a certain part of the body?
    - Does bathing or cleaning make it better?
    - Are there any associated symptoms, such as vomiting, weight loss, or lethargy?
    - Do other members of the family have similar odors?
    - Do any family members have metabolic or infectious diseases?
    - Have you seen any insertion of a foreign body in the nose, ear, anus, or vagina?
    - Has your child taken any oral or topical medications, vitamins, herbal supplements, or toxins?
    - How has the odor affected the child and family?
- Reporting by the patient of intermittent unusual odor that is never detected by others may indicate temporal lobe epilepsy with olfactory manifestations.

PHYSICAL EXAMINATION

- The examiner should
  - Note the character of the odor.
    - Physicians and patients may vary in their ability to detect certain odors and whether they are offensive.
    - If the physician notices a clearly offensive body odor but the patient or parent does not, anosmia should be considered.
  - Attempt to localize the odor to a particular body site.
  - Determine the patient's age.
  - Determine the patient's stage of pubertal development.
  - Check for other signs or symptoms during a complete examination with the child unclothed.
- Metabolic disorders should be suspected in infants with unusual body odor, especially if the infant appears ill, malnourished, or ketotic.

DIFFERENTIAL DIAGNOSIS

- The differential diagnosis of unusual odors is extensive.
  - Includes numerous systemic, metabolic, toxic, and infectious diseases
  - Can become more focused after thorough history and physical examination

Characteristic Odors, Metabolic Disease, Associated Symptoms[1]

- Cat urine
  - 3-hydroxy-3-methylglutaryl-coenzyme A lyase deficiency
    - Malaise, hypoglycemia, hepatomegaly, transaminitis, mild acidosis
- Sweaty feet, acrid, stale
  - Glutaric aciduria type II (multiple acyl-CoA dehydrogenase deficiency)
    - Hypoglycemia, hypotonia, hepatomegaly, respiratory distress, death

- Isovaleric acidemia
  - Vomiting, dehydration, coma, mild to moderate intellectual disability, aversion to protein foods
- Swimming pool
  - Hawkinsinuria (4-hydroxyphenylpyruvate dioxygenase deficiency)
    - Failure to thrive, hepatomegaly, anemia, irritability
- Boiled cabbage
  - Hypermethioninemia
    - Usually asymptomatic; some develop intellectual disability, dystonia.
  - Tyrosinemia (Odor may be like rancid butter.)
    - Liver failure, death
- Fruity, acetone-like, decomposing apples
  - Ketoacidosis (eg, from starvation or insulin deficiency)
    - Vomiting, dehydration, altered mental status, lethargy
- Maple sugar, burnt sugar, curry, malt, caramel, fenugreek, beans
  - Maple syrup urine disease (mitochondrial branched-chain α-keto dehydrogenase complex deficiency)
    - Severe form
      - Acidosis
      - Feeding difficulty, vomiting
      - Lethargy
      - Seizures
      - Coma leading to death in the first months of life
    - Intermediate form
      - Mild acidosis
      - Intellectual disability, developmental delay
      - Ophthalmoplegia
    - Intermittent form
      - Episodic ataxia and lethargy that may progress to coma
- Tomcat urine
  - Multiple carboxylase deficiency
    - Failure to thrive, hypotonia, vomiting, seizures, rash
- Dried celery, malt, hops, yeast, beer
  - Oasthouse urine disease (methionine malabsorption syndrome)
    - Diarrhea, intellectual disability, spasticity, attacks of hyperpnea, fever, edema
- Musty; similar to a mouse, horse, wolf, or barn
  - Phenylketonuria
    - Vomiting, progressive intellectual disability, microcephaly, eczema, decreasing pigmentation, seizures, spasticity
- Dead/rotting fish
  - Trimethylaminuria (fish odor syndrome)
    - Usually asymptomatic, with isolated finding.
    - Fish odor of urine and body.

Infections That Can Be Identified by Their Associated Odors[2]

- Respiratory and ear, nose, and throat infections
  - Candidiasis: sweet, fruity
  - Diphtheria: sweet
  - Intranasal foreign body: foul, putrid
  - Lung abscess, empyema, fetid bronchitis: putrid breath or sputum
  - *Pseudomonas* infections, otitis externa: foul cerumen
  - Rubella: fresh-plucked feathers
  - Tonsillitis, gingivitis, trench mouth: severe halitosis
  - Tuberculous lymphadenitis (scrofula): stale beer
  - Typhoid fever: fresh-baked brown bread
  - Yellow fever: butcher shop
- Skin infections
  - Candida (skin): heavily sweet
  - Decubitus ulcer: foul
  - Diphtheria (skin): sweet
  - Erythroderma: rancid
  - Hidradenitis suppurativa: lingering, pungent
  - Pitted keratolysis (gram-positive bacteria and dermatophytes): cheesy, sweaty, rotten smell from feet
  - *Pseudomonas* skin infection (burns): musty, fruity, grapelike, wet corn tortillas
  - Syphilis (condyloma latum): foul
  - Tinea capitis: mousy, mouse urine
- Genitourinary infections
  - Bacterial vaginosis: amine, fishy vaginal discharge
  - Genital warts (condyloma acuminatum): foul
  - Urinary tract infection with urea-splitting bacteria: ammoniacal urine
  - Vaginal foreign body, vaginitis: foul vaginal discharge
- Gastrointestinal infections
  - Rotavirus gastroenteritis: foul
  - Shigellosis: rancid stool
- Neurologic infections
  - *Cryptococcus* meningitis: alcohol smell to cerebrospinal fluid

- Miscellaneous infections
  - Chorioamnionitis: foul-smelling amniotic fluid
- Infectious etiologic agents
  - Anaerobic bacteria: foul-smelling wound, rotten apples
  - *Candida* infection: sweet, fruity, beer odor in peritoneal dialysate
  - Clostridium gas gangrene: rotten apples
  - Proteolytic bacteria: pus that smells similar to feces or overripe cheese
  - Proteus infection: mousy
  - *Pseudomonas aeruginosa*: musty, fruity, grapelike, wet corn tortillas

Recognizable Odors on the Breath Indicating Ingestion of Poisonous Substances or Toxins

- Bitter almond: cyanide (chokecherry, apricot pits), jet berry bush
- Burned rope: marijuana
- Camphor: naphthalene (mothballs)
- Carrots: water hemlock (cicutoxin)
- Coal gas: carbon monoxide
- Disinfectant: phenol, creosote
- Fishy: zinc or aluminum phosphide
- Fruity, acetone, or decomposing apples: lacquer, salicylates, chloroform
- Fruity, alcohol: alcohol (ethanol, isopropyl alcohol), phenol, acetone, amyl nitrite (poppers)
- Fruity, pear-like: chloral hydrate, paraldehyde
- Garlic: arsenic; also phosphorus, tellurium, parathion, malathion, dimethyl sulfoxide, selenium
- Glue: toluene, solvents (huffing)
- Rotten eggs: hydrogen sulfide thiol, disulfiram, dimethyl sulfate, *N*-acetylcysteine
- Severe bad breath: amphetamines
- Shoe polish: nitrobenzene
- Stale tobacco: nicotine
- Violets: turpentine
- Wintergreen: methyl salicylate

Other Conditions Associated With Specific Odors

Systemic Diseases

- Hepatic failure
  - Breath: musty fish, raw liver, feces, rotten eggs, or newly mown lawn clover (*Fetor hepaticus* caused by thiol such as dimethyl sulfide)
- Ketoacidosis (diabetes or starvation)
  - Breath: fruity, acetone-like, decomposing apples (caused by ketones)
- Uremia
  - Urine: fishy (caused by dimethylamine and trimethylamine)
  - Breath: ammoniac (caused by ammonia)

Vitamin Deficiencies

- Pellagra (niacin deficiency)
  - Breath: sour or musty
- Scurvy (vitamin C deficiency)
  - Breath: putrid

Dermatologic Conditions

- Psoriasis (pustular)
  - Skin: heavy
- Skin diseases with protein breakdown (pemphigus)
  - Skin: foul, unpleasant

Gastrointestinal Conditions

- Malabsorption
  - Feces: foul
- Melena (gastrointestinal bleeding)
  - Feces: foul

Surgical Conditions

- Esophageal diverticulum
  - Breath: feculent, foul
- Intestinal obstruction
  - Breath: feculent, foul
  - Vomitus: feculent
- Nasal foreign body
  - Nasal cavity: fetid, putrid
- Peritonitis
  - Vomitus: fecal
- Portacaval shunt, portal vein thrombosis
  - Breath: sweet

LABORATORY EVALUATION

- Infants with odor and other findings suggesting underlying metabolic disorder may need laboratory evaluation based on the suspected metabolic disease.

DIAGNOSTIC PROCEDURES

- Gas-liquid chromatography allows more precise identification of odors.
- Artificial noses or bioelectronic noses have been used to detect
  - Tuberculosis
  - *Helicobacter pylori* infection
  - Urinary tract infections
  - Bacterial vaginosis
  - Diabetes

TREATMENT APPROACH

- Once an odor is identified and evaluated, a proper diagnostic and treatment plan can begin.
- Treatment is based on the underlying condition.

SPECIFIC TREATMENT

- Osmidrosis axillae or axillary apocrine bromhidrosis can be treated by
  - Topical interventions
  - Surgical excisions
- Conditions associated with foot odor may respond to a combination of
  - Moisture control
  - Topical antibiotics
  - Antifungal agents

WHEN TO REFER

- Infants with odor and other findings suggesting underlying metabolic disorder
  - A specialist in metabolic diseases should be consulted.
  - An appropriate diet should be started while a more thorough metabolic evaluation is being completed.

WHEN TO ADMIT

- Infants with odor and other findings suggesting underlying metabolic disorder and symptoms or signs of failure to thrive, hypoglycemia, or other complications

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DEFINITION

- Oppositional defiant disorder (ODD) falls under the classification of disruptive disorder, impulse control disorder, and conduct disorder (CD).
  - Remember, this behavior is normal in 2- and 3-year-olds and early adolescents.
  - It only becomes a problem when it interferes with day-to-day functioning and is significantly different from that of peers.
- ODD encompasses a broad range of acting-out behavior toward parents and teachers.
- Behaviors associated with ODD have been shown to have potent and negative effects on child–adult and child–peer relationships.
- In the *Diagnostic and Statistical Manual of Mental Disorders*, 5th Edition (*DSM-5*), ODD indications are a pattern of
  - Angry or irritable mood, argumentative or defiant behavior, vindictiveness
  - Lasting ≥6 months
  - Exhibited in interactions with someone other than a sibling
  - Leading to poor functioning in school, at home, or in both locations
- CD.
  - Most children diagnosed with CD exhibit behaviors associated with ODD concurrently or at an earlier age.
  - Approximately two-thirds of children diagnosed with ODD do not subsequently develop CD.
- Behaviors associated with ODD often precede more serious forms of psychopathology, including CD and adult antisocial personality disorder.
  - Thus, presentation of ODD represents an opportunity for prevention efforts.

DIFFERENTIAL DIAGNOSIS

- *DSM-5* precludes a diagnosis of ODD in children who meet criteria for CD, so clinically significant oppositional behaviors may be overshadowed by diagnosis of CD (**Box 1**).
  - First, if the 2 disorders are assessed independently, each shows distinct age profiles.
    - Rates of ODD remain stable from latency through mid-adolescence, whereas rates of CD increase in teens.
  - Second, most children with CD also showed high oppositionality that does not change with age.
  - Third, when comorbidity was evaluated with other disorders
    - Attention-deficit/hyperactivity disorder (ADHD) and anxiety disorders seemed more strongly linked with ODD than with CD symptoms.
    - Depression was not linked with CD.
- Conditions that may mimic or co-occur with ODD include[1]
  - ADHD
    - Common comorbidity
      - Association of ODD and ADHD confers a poorer prognosis, and children tend to be more aggressive, have more behavior problems that are more persistent, suffer peer rejection at higher levels, and have more significant academic underachievement.
  - Sleep deprivation
    - Can cause irritability and contribute to outbursts of anger and poor impulse control
  - Learning problems or disabilities
    - Unidentified learning difficulties can contribute to frustration and oppositionality.
    - If disruptive or aggressive behavior is associated with problems of school performance, the child may have a learning disability.
  - Developmental problems
    - Overall intellectual or social limitations may be associated with frustration and poor impulse control.
    - Academically gifted children may find academic placement unstimulating and may exhibit disruptive behavior (eg, persistently annoying and distracting others, refusing to comply with teachers' requests) as a result.
  - Exposure to adverse childhood experiences (ACEs)
    - Experiencing or witnessing trauma, violence, a natural disaster, separation from a parent, parental divorce or separation, parental substance use, neglect, or physical, emotional, or sexual abuse poses high risk for developing emotional difficulties, such as adjustment disorder or posttraumatic stress disorder (PTSD), and may manifest as outbursts of disruptive or aggressive behavior; this possibility should always be borne in mind because PTSD requires specific trauma-focused interventions.

Box 1. *DSM-5* Diagnostic Criteria for Oppositional Defiant Disorder

A. A pattern of angry or irritable mood, argumentative or defiant behavior, or vindictiveness lasting at least 6 months as evidenced by at least 4 symptoms from any of the following categories, and exhibited during interaction with at least 1 individual who is not a sibling.

ANGRY OR IRRITABLE MOOD
1. Often loses temper
2. Is often touchy or easily annoyed
3. Is often angry and resentful

ARGUMENTATIVE OR DEFIANT BEHAVIOR
4. Often argues with authority figures or, for children and adolescents, with adults
5. Often actively defies or refuses to comply with requests from authority figures or with rules
6. Often deliberately annoys others
7. Often blames others for his or her mistakes or misbehavior

VINDICTIVENESS
8. Has been spiteful or vindictive at least twice within the past 6 months

Note: The persistence and frequency of these behaviors should be used to distinguish a behavior that is within normal limits from a behavior that is symptomatic. For children younger than 5 years, the behavior should occur on most days for a period of at least 6 months unless otherwise noted (criterion A8). For individuals 5 years or older, the behavior should occur at least once per week for at least 6 months unless otherwise noted (criterion A8). Although these frequency criteria provide guidance on a minimal level of frequency to define symptoms, other factors should also be considered, such as whether the frequency and intensity of the behaviors are outside a range that is normative for the individual's developmental level, gender, and culture.

B. The disturbance in behavior is associated with distress in the individual or others in his or her immediate social context (eg, family, peer group, work colleagues), or it has a negative effect on social, educational, occupational, or other important areas of functioning.

C. The behaviors do not occur exclusively during the course of a psychotic, substance use, depressive, or bipolar disorder. Also, the criteria are not met for disruptive mood dysregulation disorder.

Specify current severity:

Mild: Symptoms are confined to only 1 setting (eg, at home, at school, at work, with peers).

Moderate: Some symptoms are present in at least 2 settings.

Severe: Some symptoms are present in ≥3 settings.

From American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders.* 5th ed. Arlington, VA: American Psychiatric Association Publishing; 2013, with permission.

  - Tactfully explore the possibility that harsh physical or emotional punishment is related to or escalates the behavior problem or that tensions might escalate to that point.
    - Denial of trauma symptoms does not mean trauma did not occur; questions about ACEs should be repeated as trust is established.
- Bereavement
  - Most children will experience the death of a family member or friend sometime in their childhood.
  - Other losses may trigger grief responses (eg, separation or divorce of parents, relocation, change of school, deployment of a parent in military service, breakup with a girlfriend or boyfriend, remarriage of a parent).
  - May result in feelings of sadness, despair, insecurity, anger, or anxiety immediately following the loss and, in some instances, more persistent anxiety or mood problems, including PTSD or depression.
  - In some children, such losses trigger aggressive or disruptive behavior.
- Anxiety
  - When faced with demands that make them anxious, children may use oppositional behavior to manage anxiety or avoid the expectations that triggered their anxiety.
- Depression or bipolar disorder
  - Marked sleep disturbance, disturbed appetite, irritability, low mood, or tearfulness could indicate depression.

  - Symptoms of depression rapidly alternating with cycles of agitation may suggest symptoms of bipolar mood disorder.
    - Explosive or destructive tantrums
    - Dangerous or hypersexual behavior
    - Aggression, irritability, bossiness with adults
    - Driven creativity (sometimes depicting graphic violence)
    - Excessive talking
    - Separation anxiety
    - Chronic depression
    - Sleep disturbance
    - Delusions, hallucinations, psychosis
    - Talk of homicide or suicide
- Substance use
  - All children exhibiting disruptive or aggressive behavior should be screened for substance use and substance use disorder.
  - Drug effects or withdrawal may cause irritability and reduced self-control.
- Autism spectrum disorder
  - Problems with social relatedness (eg, poor eye contact, preference for solitary activities), language (often stilted), and range of interest (persistent and intense interest in a particular activity or subject)
  - Rigid expectations for routines or parent promises with resulting anxiety or anger if expectations are not met
- Medical problems
  - Hearing loss
  - Vision problems
  - Medication side effects
  - Neurologic disorders

DIAGNOSTIC APPROACH

- Primary care physicians need to be alert to opportunities for early detection and intervention.
  - Especially for preschoolers because efficacious treatments exist
- Important to note that regular pediatric visits have identified no possible medical complications.
- *Assessment* can be defined as identifying and understanding compatibility between a child and his or her environment.
  - Situational analysis of details contributing to oppositional moments and the incompatibility that initiates such exchanges
    - With whom is the child interacting when oppositional episodes occur?
    - What are the cognitive demands or expectations precipitating oppositional episodes and how is this understood in terms of compatibility?
    - What are specific antecedents, triggers, or conditions under which the behavior occurs?
- Gather detailed information, including
  - Developmental history of early temperament, trauma history, attachment history, and family history
  - School history of academic as well as social-emotional presentation
  - Treatment history, including previous medical and nonmedical interventions and their effectiveness
- If the oppositional behavior possibly results from lagging skills and incompatibility in the interaction between adult and child, consider formal and informal assessment of general cognitive, executive functioning, language processing, social, and problem-solving skills.
- See Diagnostic Procedures section for a list of standardized questionnaires that can be used to aid in diagnosis.

LABORATORY FINDINGS

- There are no specific laboratory studies used to make the diagnosis of ODD.

IMAGING

- There are no specific imaging studies used to make the diagnosis of ODD.

DIAGNOSTIC PROCEDURES

- Assessment measures
  - Conners Rating Scales
  - SNAP-IV (revision of Swanson, Nolan, and Pelham Questionnaire)
  - The Eyberg Child Behavior Inventory
  - Child Behavior Checklist
  - Pediatric Symptom Checklist
  - Child Symptom Inventory
  - Thinking Skills Inventory
  - American Academy of Pediatrics (AAP) mental health Initiatives
    - Resources for helping manage mental health concerns
  - NICHQ Vanderbilt Assessment Scales (for children 6–12 years of age)
    - Parent Informant
    - Teacher Informant

- Modified Overt Aggression Scale
  - For adults, but has been used with adolescents
- Strengths & Difficulties Questionnaires
- *Straight Talk About Psychological Testing for Kids*
  - Book explaining how formal neuropsychological testing can be useful in attention or learning challenges
- Bright Futures in Practice: Mental Health
  - Tools for early identification of behavioral problems.
  - This site also breaks down normative behavior by developmental stage.

CLASSIFICATION

- Mild: Symptoms are confined to only one setting (eg, at home, at school, at work, with peers).
- Moderate: Some symptoms are present in ≥2 settings.
- Severe: Some symptoms are present in ≥3 settings.

TREATMENT APPROACH

- Following assessment and diagnosis of ODD, referral to a mental health physician or nonphysician clinician should be considered.
  - The most effective treatment model is *comanagement,* in which the pediatrician maintains contact with the mental health specialist and the family.
  - Families, educators, and physicians (pediatrician and mental health specialist) as a team should be engaged in care.
- Initial interventions to try before a more formal treatment include
  - Promote daily positive joint activities between parents and child or teen.
    - Encourage counting the number of meals eaten together for a week, and try and increase it each week.
    - Media-free/electronic-free time.
    - Create a schedule of age-appropriate/developmentally appropriate daily expectations with rewards for completing.
  - Encourage parents to focus on prevention.
    - Remove activities or avoid situations that lead to challenging behaviors.
    - Avoid power struggles.
      - Example: Do not add time to the time-out for arguing about going to his or her room; instead, state, "The time will start when you get to your room."
    - Pick their battles.
    - Prioritize the things they really need their child to do.
  - Encourage parents to be calm.
    - Taking a break when feelings escalate is good role modeling.
    - Praise the child for taking a time-out to prevent overreacting.
  - Encourage parents to be consistent.
    - Set age-appropriate limits and consequences and enforce consistently.
  - Create a safety and emergency plan.
- Treatment strategies recommended by the AAP include
  - Behavioral programs for home and school.
    - Parent management training programs: Help parents and others manage a child's behaviors.
      - Positive parenting techniques and self-care
      - Individual psychotherapy: Develop more effective anger management.
      - Family psychotherapy: Improve communication and mutual understanding.
      - Cognitive problem-solving skills training (PSST): Assist with problem-solving and decrease negativity.
      - Social skills training: Increase flexibility and improve social skills and frustration tolerance with peers.
  - Consider medication for comorbid mood disorder, anxiety, or impulsiveness.
- See Specific Treatments section for more details and a discussion on use of medication.

SPECIFIC TREATMENTS

- Treatment with psychotherapy is preferable to treatment with medication in children and teens.
- Because some children with ODD go on to develop CD, there is a significant need for early identification and intervention.

Evidence-Based Psychosocial Treatments (Listed by the AAP Under "Best Support")[2]

- Anger control training
  - Cognitive behavioral therapy–style treatment for elementary school-aged children based on the social information processing model.
  - Children meet one time a week in groups of 6, usually during the school day.
  - Children discuss vignettes of social encounters with peers and possible social cues and motives of individuals in the vignettes.

- Focus is learning to increase awareness of feelings and problem-solving in situations designed to arouse anger.

- Group assertiveness training
  - Based on the verbal response model of assertiveness
  - Group treatments led by a peer or counselor
  - 8 hours of assertiveness training with treatment groups of 6 adolescents meeting twice a week for 4 weeks
- Multisystem therapy
  - Intensive family- and community-based treatment.
  - Addresses the externalizing behaviors of youth who display emotional and behavioral disturbances.
  - Average of 50 hours of direct family-based treatment over a 4- to 6-month period.
  - Home-based model targeting children and adolescents aged 12–17 years at high risk of out-of-home placement and their families.
  - Therapists work nontraditional hours and are on call for their families 7 days per week around the clock.
  - Pragmatic and goal-oriented treatment, targeting factors in each youth's social network that are contributing to problematic behavior.
  - Interventions are delivered in the natural environment and aim to develop youth competence by improving relationships, interactions, and skills of those who surround the youth.
- Parent training or behavior management training (PMT)
  - A mental health professional helps develop parenting skills that are more positive and less frustrating.
  - Treatment sessions include instruction in social learning principles and techniques.
  - Procedures and interaction patterns practiced in the sessions are then used at home.
  - Parents are usually taught how to define, observe, and record behavior at the beginning of treatment so that reinforcement and punishment techniques can be applied.
- Parent-child interaction therapy
  - Evidence-based treatment for families with children 2–6 years old.
  - 2 phases of training are
    - Child-directed interaction: Parents are trained in nondirective play skills to alter the quality of parent-child interactions.
    - Parent-directed interaction: Teaches parents to give clear instructions, offer praise for compliance, and administer time-outs for noncompliance.
  - Therapists actively coach parents while they interact with their children.
  - Sessions are one time per week for an average of 12–16 weeks.
- PSST
  - Behavioral treatment designed for children aged 7–13 years.
  - Children are taught problem-solving strategies to apply to real-life problems.
  - In-session practice to help develop skills, identify the problem, generate solutions, weigh pros and cons, make a decision, and evaluate outcomes.
  - Methods such as token response cost (tokens for good behavior that can be cashed in for a prize), corrective feedback, and social reinforcement.
  - ~25 sessions lasting 40–50 minutes, conducted with the child and occasional parent contact.
- PSST and PMT
  - Combined format; the 2 types of training are provided individually to children and parents rather than in a group.
  - Child and parent components occur concurrently, and parents and children are each informed of what the other is learning.
- Collaborative problem-solving (CPS)
  - Cognitive behavioral model that posits that chronic and severe externalizing behavior is the product of incompatibility between a child's skill set and demands placed on him or her by the environment.
  - Philosophy of CPS is that challenging children lack the thinking skills required to behave adaptively.
    - Skill deficits in critical areas such as flexibility, social perception, executive functioning, language processing, or emotion regulation
  - Intervention focuses on improving skills rather than increasing the motivation to comply.
  - The Thinking Skills Inventory is used to identify specific deficits along with the situations in which these lagging skills cause difficulty meeting adult expectations.
  - A simple framework of 3 options (referred to as plan A, plan B, and plan C) is provided for adults to decide how best to respond to chronic problems and unmet expectations.

- Interventions are tailored to assist a child in developing the skills in the context of problem-solving in a natural setting.
- Family therapy designed for ages 4–18 years.
- Primary benefits include a reduction in observed oppositional and defiant behaviors and related disciplinary interventions.
- Secondary benefits include a reduction in adult stress, improvements in adult-child relationships, and decreased staff and patient injuries.

Medication

- No single drug or regimen is indicated for the core symptoms of ODD, although ODD symptoms often improve with appropriate treatment of a comorbid condition (eg, ADHD).
  - Improvement in symptoms may inappropriately be attributed to medications instead of stabilization in the child's environment.
  - If ODD is comorbid with ADHD and ameliorated with the regimen within the first-line drugs, the pediatrician can follow medications while the psychologist, educators, and parents address the psychosocial interventions.
- Stimulants: Methylphenidate and amphetamine are first-line treatment of ADHD.
  - Such stimulants are considered even when oppositionality and aggression are present. (See Attention-Deficit/Hyperactivity Disorder for more detailed discussion of treatment).
  - An amphetamine should be considered if the initial trial with methylphenidate fails to provide adequate improvement, and vice versa.
- α-Adrenergic agonists are second-line treatment for ADHD.
  - Clonidine and guanfacine may be used initially when ADHD, ODD, and tic disorders are comorbid.
  - α-Adrenergic agonists are also considered if stimulants are not helpful.
- Selective norepinephrine reuptake inhibitor atomoxetine is a second-line medication used in treatment of ADHD.
  - Although atomoxetine is well tolerated, a slower rate of titration is associated with improved tolerability, especially because target doses may need to be higher.
  - When anxiety and a tic disorder are comorbid with ADHD and ODD, consider a trial of atomoxetine first; if not effective, a stimulant may be used.
- When ODD does not improve with initial psychosocial interventions or reflects comorbidity with disorders, a child psychiatrist should be consulted.
  - To rule out other disorders and to assess and monitor medication
  - Consider need for second-line medications (eg, atomoxetine, antipsychotics, mood stabilizers, antidepressants).
- Polypharmacy is not unusual in treating the comorbidities of ODD and requires pediatricians, psychiatrists, and other caregivers to collaboratively optimize a comprehensive treatment program.

WHEN TO ADMIT

- Symptoms from any psychiatric conditions related to ODD, such as anxiety or depression, that make a child unsafe (eg, wishing harm to either self or others)
- An adverse reaction or result from a trial of medication that warrants medical stabilization
- Accidental injury resulting from severe dysregulation (eg, losing control and becoming so upset the child falls and is injured)
- Hospitalization may help provide diagnostic clarification and, in the case of comorbidity, optimize a psychopharmacologic regimen in a closely monitored setting.
- Acute changes in mental status and a new onset of severe aggression should prompt urgent evaluation and consideration of admission for medical and psychiatric assessment.
- With complex comorbidities, a child or teen may need intense treatment, such as a day program, residential facility, or inpatient admission.
- ODD with depressed mood or suicidal ideation presents an increased risk of self-injury or suicide.

WHEN TO REFER

- Second-line medications can be monitored in primary care settings, but are generally prescribed by specialists (eg, child psychiatrists, specialists in neurodevelopmental disabilities or adolescent medicine, pediatric neurologists, adult psychiatrists with training in adolescent psychiatry).
- A pediatrician and mental health physician need to consider whether aggression is a reaction to an abusive situation that would prompt referral to child protective services.

- The AAP suggests involving a mental health specialist immediately if indicated by the following:
  - Child is <5 years.
  - Child's problems do not respond to primary care intervention.
  - Family is struggling to maintain a calm, consistent, or safe environment.
  - Child's behaviors are injurious to other children, himself or herself, or animals.
  - Child has comorbid depression.
  - Child has comorbid anxiety (the combination of shyness, anxiety, and behavior problems is thought to be risky for future behavior problems).
  - School problems are interfering with academic success and friendships.
  - Child or teen is involved with legal authorities.

FOLLOW-UP

- ODD, regardless of the presence of CD, is a highly comorbid condition with the potential for negative outcomes.
- Making sure parents and teachers are working to develop a child's skills, rather than becoming more punitive, to manage challenging behavior in an ongoing effort.

COMPLICATIONS

- ODD is frequently comorbid with other psychiatric disorders and often precedes the development of CD, substance use disorder, and severe delinquent behavior.
- ~65% of children diagnosed with ADHD meet criteria for comorbid ODD, and >80% diagnosed with ODD meet criteria for comorbid ADHD.
- In one study, nearly 70% of children with severe depression and 85% of children with bipolar disorder were also diagnosed with ODD.
- Another study found that >60% of youth diagnosed with ODD had comorbid anxiety disorder, and 45% of children diagnosed with anxiety disorder had comorbid ODD.
- Problems with schoolwork (eg, refusal to take tests, forgetting to hand in homework, misplacing books, not participating in class, being unable to settle down) may be a result of deficits in crucial thinking skills related to ODD.

PROGNOSIS

- Earlier onset of ODD symptoms conveys a poorer prognosis in terms of progression to CD—those who have early-onset ODD (<8 years) have a 3-fold increase in CD.
- There is emerging evidence that psychiatric diagnoses can be reliably ascertained in preschool populations; however, approximately half of all children who meet criteria for ODD as preschoolers will have no psychiatric problems by age 8 years.
- CD symptoms are the most robust predictor of severe and persistent forms of antisocial behavior, but ODD symptoms also predict persistent involvement in the juvenile justice system even when controlling for co-occurring CD symptoms.
- ODD and ADHD symptoms independently predicted increases in conduct problems over time as well as the development of internalizing and social problems.
- By the time children diagnosed with ODD are at the end of elementary school, ~25% will have disabling mood or anxiety problems.
- Children who meet criteria for ODD are ~4 times more likely to meet criteria for a personality disorder when they grow up than those who do not carry this diagnosis (~15% chance).
- Later in life, ODD can develop into CD, which, in turn, may develop into passive-aggressive personality disorder or antisocial personality disorder.
- By the time preschoolers diagnosed with ODD are 8 years old, only 5% still meet criteria for ODD and nothing else.
- About 5%–10% of preschoolers with ODD will eventually meet criteria for ADHD with signs of ODD.
- As is the trend with so many psychiatric disorders, the earlier ODD is diagnosed and the pediatrician helps develop an accurate understanding with the parents of the child's challenges, the more likely the child is to progress developmentally to the point of no longer meeting criteria for ODD.

PREVENTION

- Urge parents to spend dedicated one-on-one time with their child.
- Set developmentally appropriate and realistic expectations with their preschooler and work to help build their problem-solving, flexibility, and frustration tolerance skills.

- Accurate and compassionate understanding of developmental problems in these areas can prevent cycles of punitive responses to challenging behavior.

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Osteomyelitis

DEFINITION

- Infection of bone that can be acute or chronic.
- Chronic osteomyelitis may occur if
  - Infection is indolent.
  - Diagnosis is delayed.
  - Treatment does not completely eradicate infection.
- Chronic multifocal osteomyelitis is a recurring inflammatory disease not typically associated with infection that can mimic bacterial osteomyelitis.

SIGNS AND SYMPTOMS

- Chronic osteomyelitis.
  - Symptoms may have been present for months.
  - Nonspecific malaise.
  - Poor appetite.
  - Nonspecific pain in the area of the bone.
- Acute osteomyelitis.
  - Bone pain and fever
  - Open fracture or bone surgery followed by fever and new pain or drainage at the site
  - Open or closed fracture followed by new or worsening pain under a cast
- Infection causing bacteremia.
  - History of high fever spike before the onset of pain
  - Signs of bacteremia
    - Chills and high fever
    - Malaise
    - Acute illness
- Vital signs
  - May be normal, especially with chronic infection.
  - May be abnormal if child is bacteremic.
  - Fever (may be low grade) is often present.
- Local signs.
  - Localized pain is almost always present.
  - Tenderness is often exquisite; in younger children, a new limp or absence of movement of an arm or leg.
  - Inflammation, including swelling, redness, and warmth over the involved bone; this can be confused with cellulitis.
  - Reluctance to move the adjacent joint and to bear weight when a lower extremity is involved.
  - In the young infant, loss of active movement in an extremity may be confused with a neurologic problem (pseudoparalysis).
  - Erythema over the infected bone and tenderness to palpation or movement.
    - If associated arthritis occurs, pain on movement of the joint may be prominent.
  - Chronic osteomyelitis can result in a spontaneously draining sinus.
- Gastroenteritis and *Salmonella* infection may present with new fever and bone pain.

DIFFERENTIAL DIAGNOSIS

- Trauma
  - If fever is not prominent, osteomyelitis is likely to be confused with trauma or other conditions not caused by infection.
- Intra-abdominal infection, especially in the area of the psoas muscle
  - Hip or femur pain can be confused with intra-abdominal infection.
  - Chronic appendicitis can result in a phlegmon, causing a limp that can be confused with osteomyelitis of the femur.
- Osteomyelitis, septic arthritis, and juvenile idiopathic arthritis
  - All could be signaled by limp.
  - Limp necessitates careful abdominal examination.
- Back pain and diskitis
  - Diagnostic considerations must include vertebral body infection, with or without nearby epidural abscess and diskitis.
- Leukemia
  - Bone pain can be a presenting symptom of leukemia.
  - Abnormal blood cell count with anemia, low leukocyte count, or thrombocytopenia signal possible leukemia.
- Lymphoma or other cancer
  - Can be confused with osteomyelitis caused by cat-scratch disease
- Bone tumors
  - Can cause nonspecific bone pain and lytic bone lesions on radiograph.
  - To differentiate from osteomyelitis, biopsy and culture the bone.
- Septic arthritis
  - May coexist with osteomyelitis, especially in infants
  - Requires prompt treatment
- Cellulitis
  - Difficult to differentiate from osteomyelitis because of erythema over the infected bone
- Chronic multifocal osteomyelitis
  - Diagnosed over time by observing recurring disease, usually with cultures that are negative for acute infection
  - Typical radiologic appearance

DIAGNOSTIC APPROACH

- Careful examination seeking focal areas of tenderness.
  - Young child who may not be able to describe pain adequately.
  - Ask about trauma, fracture, or orthopedic surgery.
- Infants with signs and symptoms of septic arthritis of the hip must be evaluated for accompanying osteomyelitis of the femur.
  - If child is >1 year, infection tends to be held in place by the metaphysis.
  - After infancy, infection is most likely to spread into the diaphysis and down the bone.
- Blood culture and a needle aspirate of the infection site are the most helpful procedures.
  - If history and examination fit the diagnosis and a blood culture result is positive, therapy can be started without bone aspiration.
- Evaluation for related arthritis is crucial.
  - Metaphyseal osteomyelitis can progress into septic arthritis, especially in joints with intra-articular metaphysis.
  - Joint infections can progress rapidly and need emergent adequate irrigation and debridement to avoid damage.

LABORATORY FINDINGS

- Complete blood cell count and smear review.
  - Leukocyte count may be elevated in acutely ill children with bacteremia.
  - Very low leukocyte counts occur with sepsis.
  - Anemia, low leukocyte count, or thrombocytopenia in the absence of disseminated intravascular coagulation should raise concern for leukemia or other cancer.
- Erythrocyte sedimentation rate
  - May be normal at first but almost always becomes elevated in acute osteomyelitis
- C-reactive protein.
  - Usually elevated early
- Blood cultures.
  - Helpful in identifying the presence and cause of bacteremia.
  - Positive result in 40%–50% of cases.
  - Procalcitonin has been studied as a specific marker for differentiating acute osteomyelitis and septic arthritis from viral and noninfectious inflammatory bone and joint infections.
  - If infection with tuberculosis is suggested by history or setting, include cultures for acid-fast bacteria and tuberculin skin testing.
- All tests can produce normal findings, especially early in the infection.

IMAGING

- Radiography.
  - Early: no bone changes seen.
  - Earliest detectable signs are blurred soft-tissue planes secondary to edema spreading into fatty tissues.
  - Bone changes are apparent ≥7–10 days after onset of symptoms.
    - Nonspecific periosteal reaction; lytic lesions occur later.
    - Chronic osteomyelitis shows extensive disease, usually along the diaphysis of the bone.
    - Bone changes may need to be differentiated from cancer by history, cultures, and biopsy.
  - Radiographs should always be obtained to exclude other abnormalities, such as fracture or malignancy.
- Magnetic resonance imaging (MRI) is better than skeletal scintigraphy (technetium bone scan).
  - Provides excellent views of bone and soft-tissue anatomy.
  - Reveals subperiosteal abscesses that require surgical intervention.
    - Subperiosteal abscess is diagnostic for acute osteomyelitis that has broken through the metaphyseal cortex.
  - MRI is the imaging technique of choice when osteomyelitis is suspected.
- Bone scans.
  - Not useful in neonates because of low bone mineralization.
  - Provide limited information about soft-tissue involvement, subperiosteal space, and bone marrow edema.
  - Results may be normal in up to 20% of children during first days of illness.
  - Cancer, cellulitis, trauma, and bone infarction can affect specificity.
    - 3-stage scans improve sensitivity.
  - Require large amounts of radiation but no sedation or general anesthesia.
  - Can be useful in cases of suspected multiple sites of osteomyelitis.
  - Less sensitive and specific than MRI and often difficult to interpret.
- Ultrasonography.
  - Can detect a subperiosteal abscess.
  - May help guide needle aspiration of infected bone.

- Can help evaluate a nearby joint for an effusion present with an associated arthritis.

DIAGNOSTIC PROCEDURES

- Aspiration
  - Confirms diagnosis
  - Can determine necessity for operative decompression if frank pus is obtained
  - May alleviate pain caused by pressure from an abscess
  - Provides a specimen for pathogen identification by culture and material for immediate Gram stain
  - Needle aspiration of the subperiosteal space and of the metaphysis for culture is indicated to obtain culture identification of the pathogen
    - When blood cultures are pending
    - Whenever a collection of pus exists

TREATMENT APPROACH

- Acute osteomyelitis should be aggressively treated to decrease the risk of chronic osteomyelitis.
- Chronic infection requires surgical drainage or debridement and is more difficult to eradicate.
  - Antibiotics for up to 1 year
- Surgery
  - Should be prompt when indicated. Most early uncomplicated hematogenous osteomyelitis is treated by antibiotics alone, and surgery is not required.
  - Antibiotics should be started as soon as culture material is obtained.
- Once blood cultures and needle aspiration have been performed, intravenous (IV) antibiotics should be given empirically.
- Antibiotics
  - Should be adjusted once cultures and sensitivities are available, narrowing the spectrum to cover the pathogen.
  - Should be continued for 4–8 weeks, using clinical response and sedimentation rate to guide length of therapy.
  - Oral antibiotics can be considered to finish the course of therapy if
    - An oral agent is available that has good bone penetration.
    - An oral agent has excellent activity against the pathogen.
    - Oral medicine is palatable.
    - The child has a social situation that will guarantee compliance.
  - The switch to oral therapy should not occur before clinical response to IV therapy, including
    - Absence of fever
    - Return to normal function
    - Decrease or normalization of inflammatory markers
  - Oral antibiotics often require 2–3× the usual dose, making gastrointestinal tolerance a requirement.
  - Therapy is sometimes prolonged by several weeks empirically.
- Abscess
  - Must be drained surgically when detected or suspected.
  - Lack of pus should suggest that the aspiration site may have been inaccurate or that pus may be present but too thick to pass through a large-bore needle.
  - Chronic osteomyelitis requires surgical debridement to remove necrotic bone and prolonged antimicrobial therapy typically lasting 3–6 months.

SPECIFIC TREATMENTS

Pharmacologic Therapy

- After the newborn period, in a previously well child thought to have hematogenous osteomyelitis, give a penicillinase-resistant penicillin or first-generation cephalosporin unless
  - The child is severely ill.
  - The child has signs of bacteremia and sepsis.
    - If the child has sepsis, vancomycin should be considered because of the increasing incidence of methicillin-resistant *Staphylococcus aureus* (MRSA).
- Therapy should cover all likely pathogens.
  - In newborns, initial therapy should always include coverage against gram-negative enteric organisms.
    - Oxacillin and gentamicin.
    - Vancomycin and ceftazidime.
      - When concern about MRSA infection exists
      - For coagulase-negative staphylococci
    - Neonates who have been in a neonatal intensive care unit and who have been on antibiotics should be treated most broadly, pending culture results.
- Antifungal agents are not usual unless blood culture or other epidemiologic data suggest fungal infection.

- Children with sickle cell hemoglobinopathies are at special risk for *Salmonella* species in addition to *S aureus.*
  - Treat with cefuroxime or with vancomycin and ceftriaxone or cefotaxime, pending culture results.
- If pseudomonal infection is suspected or there is contamination with dirt (eg, puncture wound of the foot), initial treatment should be either
  - Ceftazidime.
  - A carboxypenicillin or acyl-ureidopenicillin combined with an aminoglycoside, such as piperacillin-tazobactam and gentamicin or ceftazidime and gentamicin.
  - Piperacillin-tazobactam is appropriate to treat *S aureus* while culture results are pending.
- Clindamycin.
  - Often used in cases of allergy to β-lactams or to treat MRSA isolates that are sensitive.
  - It has been recommended as empiric therapy if MRSA is suggested, although some isolates may be resistant.
- Linezolid
  - Should not be used empirically.
  - May be helpful in patients with β-lactam allergies and as a drug that can be used orally to treat a serious infection.
  - Side effect of thrombocytopenia limits its long-term use.

WHEN TO ADMIT

- Children with acute osteomyelitis require admission to the hospital for rapid evaluation and to initiate treatment.
- Initial evaluation can begin as an outpatient, before diagnosis is established.
  - Follow up closely and consider hospitalization as soon as the diagnosis becomes likely.

WHEN TO REFER

- Diagnosis requires thorough evaluation and usually includes consultation with radiology and orthopedic surgery personnel.
  - Radiologist can help focus the radiologic evaluation effectively.
  - Early orthopedic consulting helps expedite aspiration or open drainage.
- Infectious disease specialists may help
  - To organize the evaluation
  - To start therapy
  - With follow-up with children who are discharged on home IV therapy and who have chronic disease

COMPLICATIONS

- Chronic osteomyelitis can result in lifelong disability related to recurrences and, rarely, to cancer.
- Chronic osteomyelitis may result in bone loss and areas of devascularized bone, which separate and create sequestrum or pieces of dead bone in the shaft of the long bones.
  - If this occurs, surgery will be required to treat the infection.
  - Brodie abscess capsule can develop in the bone; appears to be the result of walled-off chronic infection.
- Complications for hematogenous osteomyelitis include deep vein thrombosis (DVT), with increased risk if
  - Critical illness at presentation
  - Positive blood culture result
  - Infection with MRSA
  - Elevated C-reactive protein
  - Central venous catheter
- DVT should be considered if the patient develops pulmonary findings or has persistently positive blood culture results.
- Long-term complications may include pathologic fractures, limb length discrepancy, and avascular necrosis.
  - Risk factors include
    - Delay in diagnosis >1 week
    - Newborn age
    - Hip joint infection
    - Infection with MRSA
    - >3-day delay in treatment with appropriate antibiotic(s)

Otitis Media and Otitis Externa

DEFINITION

- *Otitis media* means inflammation of the middle ear.
- *Acute otitis media* (AOM) is the presence of inflammatory fluid in the middle-ear space, accompanied by acute onset of local findings, and an erythematous, opaque, and bulging tympanic membrane with distorted landmarks and light reflux. The tympanic membrane is not mobile on insufflation.
- *Otitis media with effusion* (OME) describes non-purulent fluid in the middle-ear space that can cause a feeling of fullness and hearing loss but usually does not have accompanying fever or pain.
  - *Serous otitis media,* a type of OME, is seen with clear, watery fluid.
- *Recurrent otitis media* has generally been used to refer to the occurrence of
  - ≥3 episodes of AOM in 6 months
  - 4 episodes in 1 year with 1 episode in the preceding 6 months
  - Recurrent otitis media should not be confused with *chronic otitis media,* which may be used to describe OME that
    - Lasts >3 months
    - Is a suppurative middle-ear process that fails to respond to initial antibiotic therapy
- *Otitis externa* is an inflammatory process that involves structures of the outer ear, specifically the external auditory canal.
- *Malignant otitis externa* is a complicated form of otitis externa that can develop in immunocompromised children and those with severe malnutrition.

SIGNS AND SYMPTOMS

Otitis Media

- In the classic case of AOM, a young child with a history of a recent upper respiratory tract infection develops acute onset of
  - New fever
  - Ear discomfort or pain
- Other symptoms include
  - Otorrhea
  - Distortion of the tympanic membrane (bulging, erythema, opacity, limited mobility)
- In children old enough to localize pain, the affected ear is often obvious.
- In younger children, discomfort may be more generalized, exhibited by unexplained crying or irritability.
- Examination may reveal other signs of upper respiratory infection, such as
  - Rhinorrhea
  - Cough
  - Conjunctival injection

Otitis Externa

- Children complain of ear pain.
- May report pain with chewing.
  - Because of proximity of the temporomandibular joint to the external auditory canal
- May report difficulty hearing.
  - Result of swelling within the external auditory canal and conductive hearing loss
- Examination reveals tenderness with manipulation of the pinna or pressure on the tragus.
- Insertion of otoscope into the external auditory canal can be painful and should be undertaken carefully.
- Within the canal, focal erythema and swelling may be seen at the site of trauma or folliculitis.
- If inflammation is diffuse, swelling of the entire canal renders a boggy appearance.
- Edema and the presence of inflammatory debris may prevent complete visualization of the tympanic membrane.
- The tympanic membrane should appear normal in otitis externa, unless coexistent otitis media is present.

Malignant Otitis Externa

- Pain is severe.
- Discharge from the external canal is copious and malodorous in nature.
- Patients may develop facial paralysis.

DIAGNOSTIC APPROACH

Otitis Media

- Concern is growing that overdiagnosis of otitis media and liberal use of antibiotics for treatment have contributed to the rapid emergence of antibiotic-resistant bacteria.
  - Particularly penicillin-resistant *Streptococcus pneumoniae*
- Accurate diagnosis is critical to appropriate management.
- Diagnosis is based on recognition of
  - Characteristic clinical context
  - Physical findings on pneumatic otoscopic examination

- Diagnosis of AOM is confirmed using pneumatic otoscopy.
  - To perform this technique, the child must cooperate or be restrained in a comfortable position that allows manipulation of the pinna and insertion of the otoscope into the external auditory canal.
  - Cleanse the external auditory canal for clear visualization of the tympanic membrane.
    - Cerumen or foreign bodies should be removed using a cerumen spoon or gentle irrigation with warm water.
  - The largest speculum that will fit into the external auditory canal at a depth of ⅓–½" should be attached to the pneumatic otoscope.
    - Permits visualization of the largest possible area and ensures a relatively airtight seal for insufflation
  - AOM is present when
    - Bulging of the tympanic membrane is noted on direct visualization, often making it appear donut-like.
    - There is purulent, yellow or blue-gray fluid behind the membrane causing opacity of the membrane, obscuring normal landmarks.
    - Restricted movement of the tympanic membrane, indicative of fluid in the middle ear, may be noted with gentle insufflation and exsufflation using the squeeze bulb attached to the otoscope if a good seal is formed.
  - Erythema of the tympanic membrane alone is not sufficient to diagnose AOM.
    - Possibly the incidental result of fever or crying
  - Occasionally, a child with AOM experiences spontaneous rupture of the tympanic membrane.
    - Leads to marked improvement in ear pain.
    - Otorrhea is evident on examination.
- OME may be an incidental finding on physical examination.
  - Decreased mobility of the tympanic membrane.
  - Clear fluid behind the tympanic membrane.
  - Signs of acute inflammation seen in AOM are absent.
- Malignant otitis media should be suspected with the following signs:
  - Severe pain not controlled with over-the-counter analgesics
  - Draining purulent fluid in the canal
  - Severe headache on side of ear pain
  - Signs suggestive of nerve involvement: difficulty swallowing, hoarseness, or even facial droop

LABORATORY FINDINGS

Otitis Media

- Some experts advocate making a specific bacteriologic diagnosis, but this is generally unnecessary unless faced with recurrent, chronic otitis media (see Diagnostic Procedures section).

Malignant Otitis Externa

- Left shift on complete blood cell count may be observed.
- Erythrocyte sedimentation rate is usually elevated.
- Culture and sensitivity should be done prior to initiating treatment whenever possible.
  - In immunocompromised hosts (diabetics), *Pseudomonas* is most common.
  - In non-immunocompromised hosts, methicillin-resistant *Staphylococcus aureus* is becoming more common.
  - If culture and sensitivity results are negative and infection is refractory to treatment, consider fungal origin.

IMAGING

- Malignant otitis externa can be diagnosed by clinical signs and imaging.
  - Triphasic bone and gallium scintigraphy examinations are often used, but studies suggest that single-photon emission computed tomography images are even more sensitive.

DIAGNOSTIC PROCEDURES

- Tympanocentesis or carbon dioxide laser-assisted myringotomy.
  - Used to obtain middle-ear fluid for culture and sensitivities
  - Not necessary for routine diagnosis of AOM
  - Useful in specific clinical situations in which identification of the organism to guide therapeutic decisions is a high priority
    - Episodes of AOM that do not respond to empirical antibiotic therapy
    - Children who experience frequent recurrences despite seemingly appropriate therapy
    - Children who are young and particularly toxic in appearance
- Cultures of other areas of the upper respiratory tract are useful for research.
  - Do not assist in the management of individual episodes of AOM.

- The same organisms usually are recovered from the nasopharynx as from middle-ear fluid.
  - The presence of an organism from nasopharyngeal culture does not prove presence in the middle ear.

- Tympanometry is a technique for documenting tympanic membrane compliance.
  - Can be used to objectively document the presence of fluid in the middle-ear space.
  - Does not add to information obtained on carefully performed pneumatic otoscopy.
  - Can be useful for monitoring the course of an episode of OME over time.

TREATMENT APPROACH

- Otitis media is usually self-limited.
  - As viral illness resolves, eustachian tube function is restored.
  - The middle-ear space drains normally.
- Acute symptoms generally resolve spontaneously within a few days.
- Middle-ear effusions can persist for weeks after an episode of AOM.
  - 60% of middle-ear effusions resolve spontaneously within 3 months.
  - 85% resolve within 6 months.
- Persistence of middle-ear effusions (or OME) after an episode of AOM has raised concern about
  - Conductive hearing loss that accompanies these effusions
  - Effect on speech and language development, especially in younger children
- Effusions are sterile.
  - In the absence of other acute signs and symptoms, they do not require antibacterial therapy.

SPECIFIC TREATMENTS

Management of AOM

- When an episode of AOM should be treated with antibiotics is evolving. The 2004 American Academy of Pediatrics (AAP) guidelines were revised in 2013.
  - Bilateral or unilateral AOM in children ≥6 months with severe signs or symptoms (ie, moderate or severe otalgia, otalgia for at least 48 hours, or a temperature ≥39.0°C [102.2°F]): Prescribe antibiotic therapy.
  - Bilateral AOM in children <24 months with or without severe signs or symptoms (ie, mild otalgia for at least 48 hours, temperature <39.0°C [<102.2°F]): Prescribe antibiotics.
  - Unilateral AOM in children 6–23 months without severe signs or symptoms (ie, mild otalgia for at least 48 hours, temperature <39.0°C [<102.2°F]): Prescribe antibiotic therapy or offer observation with close follow-up based on joint decision-making with the parent(s)/caregiver.
  - Bilateral or unilateral AOM in children ≥24 months (ie, mild otalgia for at least 48 hours, temperature <39.0°C [<102.2°F]): Prescribe antibiotic therapy or offer observation with close follow-up based on joint decision-making with the parent(s)/caregiver.
- When observation is used, a mechanism must be in place to ensure follow-up and begin antibiotic therapy if the child worsens or fails to improve within 48–72 hours of onset of symptoms.
- If an antibiotic is used, choose the narrowest spectrum.
  - In population-based studies of children with AOM, the most common organisms isolated were *S pneumoniae, Haemophilus influenzae,* and *Moraxella catarrhalis.*
  - High-dose amoxicillin is the recommended first-line choice.
    - Inexpensive.
    - Good spectrum of activity against target organisms, including strains of *S pneumoniae* with intermediate resistance to penicillin at 90 mg/kg/d dosing, in divided doses twice a day.
    - Children ≤2 years and those with severe symptoms: A standard 10-day course is recommended.
    - Children between 2 and 5 years of age with mild or moderate AOM: A 7-day course can be equally effective.
    - Shorter courses of 5–7 days may be acceptable in low-risk patients (children ≥6 years with mild or moderate symptoms).
    - If it has been used in the last 30 days, consider using amoxicillin-clavulanate as first-line therapy.
    - If patient is allergic to amoxicillin, use cefdinir (14 mg/kg/d).
      - If recent cefdinir use, use cefpodoxime (10 mg/kg/d).
- If fever, ear pain, and objective findings of AOM persist despite ≥72 hours of therapy, a change of antibiotic may be warranted.
- The risk of suppurative complications is not increased with this approach.

- Treatment of pain is very important for all types of AOM.
  - Topical antipyrine and benzocaine otic solution, benzocaine, lidocaine, and procaine otic solutions can provide brief additional benefit over acetaminophen in children >5 years.
  - Acetaminophen and ibuprofen should be the mainstay of pain treatment.

Management of OME

- OME presents a different therapeutic challenge.
  - The goal of therapy is to limit potential long-term detrimental effects on speech and language development.
  - Weak associations have been found between OME and abnormal speech and language development in children <4 years.
  - Problems with attention and expressive language delay have been found in older children.
  - Associations may be the result of environmental influences that predispose patients to OME and developmental delays.
  - The effects of treating OME on these outcomes are not well established.
- Medical therapies for OME have produced unsatisfactory results.
  - Very limited scientific evidence exists.
  - Most experts strongly discourage empirical antibiotic therapy early or later, when the effusion has persisted for ≥3 months, as evidence has not shown improvement in resolution of the effusion.
    - This practice has given rise to increasing rates of antibacterial resistance.
- The most effective therapy is surgical insertion of tympanostomy tubes.
  - Placement of tympanostomy tubes evacuates middle-ear effusion and restores near-normal hearing.
    - The effect on long-term speech and language outcomes is unclear.
    - Laser-assisted myringotomy may soon replace tympanostomy tube placement.
- Adenoidectomy is used in the management of patients with OME.
  - May be effective in a select group of children.
  - Chronically infected adenoids are thought to serve as a reservoir of pathogenic organisms, leading to tubal edema and malfunction and persistent OME.
  - Removal of enlarged adenoids has been shown to improve effusion resolution.
  - Adenoidectomy and myringotomy plus ventilation tube insertion is recommended therapy for
    - Children with severe ear disease
    - Children undergoing replacement of a second set of ventilation tubes

Management of Recurrent Otitis Media

- Occurrence of ≥3 episodes of AOM within 6 months or 4 episodes within 1 year with 1 episode in the preceding 6 months.
  - Therapy is controversial.
  - Studies have shown that long-term administration of prophylactic antibiotics (usually amoxicillin or trimethoprim plus sulfamethoxazole) can reduce incidence of subsequent episodes of AOM, but the effect is very small.
    - Even long-term, low-dose antibiotic use (antibiotic prophylaxis) has prevented 1.5 episodes of AOM per year. However, an estimated 5 children would need to be treated for 1 year to prevent 1 episode of otitis media, specifically in children with ≥6 episodes of AOM in the preceding year.
    - Use of prophylactic antibiotics is currently not recommended for management of recurrent otitis media.
- Tympanostomy tube placement or laser-assisted myringotomy should be considered in the management of recurrent otitis media.
  - This approach may be justified when recurrent AOM complicates OME and is accompanied by hearing loss.
  - Frequent episodes of AOM (without OME) that respond to appropriate antibiotic therapy are not an indication.
  - AOM tends to occur less frequently in children who have had tympanostomy tubes placed.
    - Requires administration of anesthesia.
    - Tubes may not remain in place for a sufficient duration to have a measurable effect on health of an individual child.

Care of the Child With Tympanostomy Tubes

- Tympanostomy tube placement is the most common surgical procedure performed in children.
  - Examination of the child with tympanostomy tubes should show a patent tube traversing the pars flaccida.

- A tympanic membrane that contains a tympanostomy tube is not intact; therefore
  - Mobility is affected.
  - Pneumatic otoscopy cannot be used as a reliable indicator of AOM.

- Tympanostomy tubes usually extrude naturally sometime after insertion.
  - Some otolaryngologists recommend actively removing tympanostomy tubes that have been in place for ≥2 years to prevent complications, such as chronic perforation or tympanosclerosis.
  - If a tympanostomy tube is visualized in the external canal and is no longer seated within the tympanic membrane, it may be removed with a cerumen spoon under direct visualization.
- Otorrhea is common in children with tympanostomy tubes.
  - Otorrhea associated with other symptoms of upper respiratory infection may indicate the presence of AOM.
    - Treat accordingly.
  - When otorrhea occurs in isolation, it may respond to topical application of an otic solution containing
    - Neomycin
    - Polymyxin B
    - Hydrocortisone
  - Otorrhea is no more common in children with tympanostomy tubes who swim or submerge their heads in a bathtub than in those who do not.
  - Use of topical antibiotics or earplugs does not reduce incidence of swimming-related otorrhea.
  - Children with tympanostomy tubes who do not dive to depths >6 feet or swim in potentially contaminated water (eg, a pond) require no special precautions to swim.
    - Use of earplugs or molds may increase drainage from the ears.
    - Earplugs or molds should be used when swimming in ponds or lakes, which have a higher risk of contamination.

Management of Otitis Externa

- When otitis externa is accompanied by furuncle formation, incision and drainage may be necessary.
  - Diffuse otitis externa usually responds to application 4 times a day for 7–10 days of a topical otic solution containing
    - Neomycin
    - Polymyxin B
    - Hydrocortisone
  - With the patient lying on the unaffected side, 5 drops of this solution are instilled into the affected ear.
  - The patient should remain in this position for 5–10 minutes after instillation to ensure that the medication comes in contact with the affected skin.
  - Insertion of a cotton wick can prolong this contact.

Management of Malignant Otitis Externa

- Treatment requires administration of intravenous (IV) antibiotics.
- Occasionally, surgical intervention is required.

WHEN TO ADMIT

- Admit to the hospital any patient with severe otitis media who
  - Is toxic in appearance
  - Has malignant otitis externa
  - Has suppurative complications of otitis media
- Admission allows for
  - Institution of prompt, effective IV antibiotic therapy
  - Further evaluation for possible surgical intervention

WHEN TO REFER

- Patients with recurrent or chronic otitis media or persistent OME (present for at least 3 months) should be referred to an ear, nose, and throat (ENT) specialist for further evaluation.
- In addition, an infectious disease consultation should be obtained for patients with the following conditions:
  - Suppurative complications of otitis media
  - Recurrent or chronic episodes of otitis media unresponsive to standard therapy
  - Unusual or multiple antibiotic-resistant organisms isolated from middle-ear fluid
  - Chronic suppurative otitis media unresponsive to conventional therapy
  - Malignant otitis externa
- In many of these conditions, a multidisciplinary team approach with ENT and infectious disease referrals should be used for optimal management of the patient's condition.

FOLLOW-UP

- AOM treatment
  - Observation for initial management of AOM does not increase suppurative complications as long as follow-up is provided and delayed antibiotics are then begun for persistent or worsening symptoms.
  - Most children who respond satisfactorily to treatment do not require specific follow-up.
  - As long as a child is asymptomatic, the main reason for follow-up is to document resolution of a middle-ear effusion that may contribute to conductive hearing loss.
  - After 2 weeks of antibiotic therapy, 60%–70% of children can have an effusion, whereas after 4 weeks, the percentage decreases to 40%, followed by 10%–25% after 3 months of appropriate antibiotic therapy.
    - Therefore, follow-up for an otherwise healthy and asymptomatic child should be scheduled no sooner than 6 weeks post-diagnosis, if at all.
  - An effusion that is persistent at 6 weeks does not warrant specific intervention other than perhaps checking for resolution again in 6 more weeks.
- Documented OME
  - Follow-up at 3 months is reasonable, assuming that acute symptoms have not intervened.
  - If hearing is within reference range, further observation to allow spontaneous resolution is appropriate.
  - If a conductive hearing loss at a threshold ≥20 dB is documented at the 3-month follow-up, consideration should be given to tympanostomy tube placement or laser-assisted myringotomy to drain the effusions and restore hearing.
  - Use of these procedures for OME in otherwise healthy children with normal hearing is not recommended.

COMPLICATIONS

Otitis Media

- Conductive hearing loss resulting from chronic middle-ear effusions associated with otitis media may contribute to speech and language delay in some children.
- Overuse of antibiotics to treat otitis media is thought to contribute significantly to the emergence of antibiotic-resistant bacteria.
- Suppurative complications of otitis media are
  - Mastoiditis
  - Intracranial extension of infection
  - Lateral sinus thrombosis
- Early signs and symptoms associated with suppurative complications include
  - Mastoid tenderness.
  - Persistent fever associated with chronic tympanic membrane perforation.
  - Persistent and severe headache.
  - Severe otalgia.
  - Retro-orbital pain on the side of the affected ear.
  - Vertigo.
  - Mental status changes.
  - Nystagmus.
  - Other focal neurologic signs can signal intracranial extension of suppurative otitis media.
    - Facial paralysis
    - Meningismus
    - Papilledema

Malignant Otitis Externa

- Stenosis of the external auditory canal
- Auricular cartilage deformity
- Tympanic membrane necrosis
- Sensorineural hearing loss

PROGNOSIS

- Most otitis media is self-limited and resolves spontaneously in several days.
- OME: Placement of tympanostomy tubes evacuates middle-ear effusion and restores near-normal hearing.
  - The effect on long-term speech and language outcomes is unclear.
- Malignant otitis externa: Development of facial paralysis indicates a poor prognosis.

PREVENTION

- The following can help prevent the occurrence of otitis media:
  - Any amount of breastfeeding reduces the incidence of otitis media by 23%, and exclusive breastfeeding for >3 months reduces it by 50%.
    - The 2013 AAP guidelines also suggest that physicians encourage exclusive breastfeeding for at least 6 months.
    - Exclusive breastfeeding early in life has a protective effect.
  - Immunizations with influenza and pneumococcal vaccines.
  - Develop an effective RSV vaccine.
  - Avoiding passive smoke exposure.

- Using appropriate feeding positions (eg, not feeding in lying down position).
- Treating the underlying cause, such as cleft palate.
- Prophylactic antibiotics are not recommended for the prevention of AOM.
  - The number needed to treat is equivalent to 5 patients on antibiotics for 1 year to prevent 1 ear infection in children with >6 ear infections a year.

- Otitis externa can be prevented by
  - Keeping the external auditory canal dry
  - Avoiding vigorous cleaning of the canal that can lead to superficial trauma

DEFINITION

- Inflammation of the pancreas in the clinical setting of epigastric abdominal pain
- Acute pancreatitis
  - Reversible process with complete resolution of the inflammatory reaction and return of normal pancreatic endocrine and exocrine function
- Chronic pancreatitis
  - Characterized by a more prolonged and recurrent course
  - May ultimately result in irreversible changes in glandular histopathology (fibrosis) and pancreatic dysfunction
  - Occurs in ~9% of children who present with acute pancreatitis

SIGNS AND SYMPTOMS

- Upper abdominal pain and tenderness at the onset.
  - Often midepigastric or in left or right upper quadrants
  - Classic radiation to the back in some
- Concomitant symptoms include
  - Nausea
  - Vomiting
  - Low-grade fever
  - Worsening of pain with eating
- Relief of pain in the antalgic position with hips and knees flexed, sitting in the upright position, or lying on the side
- In cases of severe pancreatitis, symptoms can be particularly impressive.
  - Elevated fevers
  - Signs of shock
  - Jaundice
  - Pleural effusions
- Age and expressivity often complicate initial presentation, especially in younger children.
- Many present with a more atypical picture.
- Hemorrhagic or necrotic pancreatitis.
  - Bluish discoloration around the umbilicus (Cullen sign) or the flanks (Turner sign)
  - Rare, but often predicts a more severe clinical course with multisystem inflammatory responses and multiorgan dysfunction

DIFFERENTIAL DIAGNOSIS

- Pancreatitis is often diagnosed only after more common causes of the presenting symptoms have been considered.
  - Acute gastroenteritis
  - Appendicitis
  - Mesenteric adenitis
  - Urinary tract infections
- In severe pancreatitis, the differential must be expanded to include
  - Perforated viscus
  - Acute peritonitis
  - Biliary tract disease
  - Intestinal obstruction
- Many other disease processes can lead to elevations in the pancreatic enzymes (particularly amylase) (**Box 1**).

DIAGNOSTIC APPROACH

- Pancreatitis in children continues to be underdiagnosed.
  - A high index of suspicion for pancreatitis is appropriate in any patient with epigastric abdominal pain.
- Thorough history and physical examination are crucial to direct diagnostic studies and initial management.
- Family history is important because hereditary pancreatitis is often transmitted as an autosomal-dominant trait with incomplete penetrance.

LABORATORY FINDINGS

- Complete blood cell count with differential, renal panel with glucose, liver function studies, and pancreatic enzymes (amylase and lipase) are often obtained in the initial investigation (**Table 1**).
- Amylase.
  - Used to confirm acute pancreatitis despite its relatively low sensitivity and specificity (75%–92% and 20%–60%, respectively).
  - Levels 3× the upper limit of reference range are often used as diagnostic cutoffs for pancreatitis.
  - Serum activity increases 2–12 hours after pancreatic injury and peaks at 12–72 hours.
  - Hyperamylasemia is not diagnostic and may be secondary to various disease processes in the salivary gland, intra-abdominal pathology, or systemic disease.
  - Laboratories can separate amylase isoenzymes into pancreatic and salivary fractions.
  - Fractionation is a specialized test; long turnaround time for results may preclude its usefulness in the acute setting.
- Serum lipase.
  - During acute pancreatitis, serum lipase rises by 4–8 hours, peaks at 24–48 hours, and remains elevated longer than serum amylase.

Box 1. Conditions Associated With Elevated Serum Amylase

From Pancreatic Amylase Fraction
- Aortic aneurysm—abdominal
- Appendicitis
- Biliary duct obstruction
- Biliary tract disease
- Choledocholithiasis
- Endoscopic retrograde cholangiopancreatography
- Intestinal infarction, obstruction, or perforation
- Pancreatic duct obstruction
- Pancreatic tumors
- Pancreatitis—acute, chronic
- Perforated peptic ulcer
- Peritonitis
- Pseudocyst

From Salivary Amylase Fraction
- Anorexia nervosa
- Bulimia
- Infection (mumps)
- Lung cancer
- Ovarian tumor/cyst
- Parotitis
- Pneumonia
- Prostate tumors
- Salivary duct obstruction
- Salpingitis
- Trauma

Both (or Unknown)
- Alcoholism
- Burns
- Cardiopulmonary bypass
- Cirrhosis
- Cystic fibrosis
- Diabetic ketoacidosis
- Drugs
- Head trauma
- Hepatitis
- Heroin addiction
- Macroamylasemia
- Opiates
- Renal insufficiency
- Renal transplantation
- Ruptured ectopic pregnancy

Table 1. Common Laboratory Values in Acute Versus Chronic Pancreatitis

	Acute Pancreatitis	Chronic Pancreatitis
Complete blood cell count	Leukocytosis with bandemia hemoconcentration	Usually within reference range
Renal (glucose)	Hyperglycemia, hypocalcemia	May have elevated glucose
Liver function	Elevations in ALT, AST, alkaline phosphatase, total bilirubin	Elevated in patients with concomitant liver disease or bile obstruction
Amylase/lipase	Elevated (generally use 3–6× the upper limit of reference range)	Normal or slight elevation

Abbreviations: ALT, alanine transaminase; AST, aspartate transaminase.

- Despite its high specificity, serum lipase can be elevated in
  - Acute cholecystitis
  - Intestinal infarction
  - Perforated peptic ulcer disease
  - Renal failure
- Serum levels of these laboratory values depend on chronicity of the inflammatory process and may differ dramatically based on the clinical picture.
- Patients with chronic pancreatitis moving toward glandular insufficiency may experience exacerbations of acute pancreatitis with relatively low serum levels of amylase and lipase.
- Enzymes are often normal even during attacks of pain.
- Normal amylase or lipase levels should not exclude the diagnosis in a child with a positive history of pancreatitis.

- Gold standard for diagnosing chronic pancreatitis is glandular insufficiency.
  - Noninvasive tests assess pancreatic function (decreased serum pancreatic enzymes, fecal assays for fat and pancreatic enzymes), but the negative predictive value often limits their interpretation.
  - False-positive results may be obtained in the presence of intestinal overgrowth or other mucosal disease.
  - True establishment of pancreatic insufficiency often involves
    - Oroduodenal or endoscopic intubation
    - Accurate placement of a duodenal catheter
    - Complete recovery of duodenal secretions
  - Limited to tertiary centers.
- Other laboratory abnormalities that may be present in acute pancreatitis include
  - Coagulopathy
  - Glucosuria
  - Hypocalcemia
  - Elevated γ-glutamyl transpeptidase
  - Hyperbilirubinemia
- Biochemical markers.
  - May help predict the severity and progression of acute pancreatitis but are nonspecific and not useful in initial diagnosis.
  - C-reactive protein.
    - Most useful
    - Delayed increase, peaking not earlier than 72 hours after the onset of symptoms
    - Accurate and widely available
  - Interleukin 6.
    - Rises in severe pancreatitis in comparison with mild disease as early as the day of hospital admission
    - Peak concentrations on day 3 after the clinical onset of the disease
  - Procalcitonin.
  - Additional markers requiring further investigation include
    - Serum amyloid A
    - Trypsinogen activation peptide
    - Polymorphonuclear granulocyte elastase
  - Immunoglobulin G4 elevations may be more specific for autoimmune pancreatitis.
- Genetic testing.
  - Genetic testing can be considered diagnostic or predictive.
    - Diagnostic tests for hereditary pancreatitis are often obtained to determine genetic causes of a patient's pancreatitis.
    - Predictive testing in patients without evidence of disease but who may have relatives with known pancreatitis or genetic susceptibilities to developing pancreatitis.
    - In general, the clinical indications leading to diagnostic testing validate its use, but the role of predictive testing is more controversial.

IMAGING

- Ultrasound
  - Often the initial imaging modality
  - Findings consistent with pancreatitis
    - Glandular edema
    - Hyperechogenicity
    - Pancreatic ductal dilation
    - Pancreatic ducts with the following diameters are significantly associated with pancreatic inflammation:
      - >1.5 mm in children aged 1–6 years
      - >1.9 mm in children aged 7–12 years
      - >2.2 mm in adolescents aged 13–18 years
  - Useful in detecting causes and complications associated with pancreatitis, such as gallstones, pseudocysts, and splenic vein thrombosis
- Computed tomography (CT)
  - Animal models have shown that CT contrast material given early in acute pancreatitis may decrease blood flow and may worsen pancreatic necrosis.
  - Validation studies have not yet been done in children, but physicians should consider whether the information obtained via CT will influence medical management.
- Endoscopic retrograde cholangiopancreatography (ERCP)
  - Often useful in diagnosing.
    - Anatomic variations (eg, pancreas divisum)
    - Suspected biliary obstruction
  - Main advantage over other imaging modalities is the ability to treat an anatomic obstruction at the time of procedure.
    - Therapeutic procedures include sphincterotomies, stone removal, and stent placement in the biliary or pancreatic ductal system.
  - ERCP with glandular drainage decreases the frequency of pancreatitis episodes requiring hospitalization in certain populations, such as those with cystic fibrosis.
  - Seems to be effective and safe in children, with cannulation rates and visualization of the pancreaticobiliary duct anatomy similar to those in adults.

- Complications.
  - Iatrogenic pancreatitis (up to 11% of procedures developing a clinical picture of pancreatitis)
  - Asymptomatic hyperamylasemia in up to 70% of patients after the procedure
- Advances in magnetic resonance cholangiopancreatography (MRCP) have prompted the National Institutes of Health to advise "no role [for ERCP] in the diagnosis of acute pancreatitis except when biliary pancreatitis is suspected."

■ MRCP
- Can complement ERCP in more complicated pancreatitis for which additional investigation of ductal anatomy may be needed.
- Advantages of MRCP over ERCP include
  - Noninvasive.
  - Does not use radiation.
  - Can visualize the pancreatic parenchyma and pancreatic ducts as small as 1 mm proximal and distal to any potential obstructive lesion.
  - Secretin can be given to patients to increase pancreatic duct signal for improved studies.
- Limitations of MRCP include
  - Results vary according to patient body habitus, patient cooperation and ability to remain still (often requiring sedation), and the medical center's experience.

DIAGNOSTIC PROCEDURES

■ Pancreatic biopsy
- Rare; usually obtained in patients with a more chronic clinical course.
- Provides critical information when a diagnosis such as autoimmune pancreatitis is suspected (characteristic dense lymphoplasmacytic infiltration and fibrosis).
- Potential benefits are more specific categorization and staging of chronic pancreatitis, leading to more targeted and directed therapies.

CLASSIFICATION

■ Can be categorized according to histopathologic findings
- Edematous changes often correlate with mild disease.
- Evidence of hemorrhagic or necrotic change signifies a more severe process with increased morbidity and mortality or irreversible gland dysfunction.

TREATMENT APPROACH

■ Treatment of pancreatitis in children does not differ from that of adults.

■ Acute pancreatitis.
- Supportive treatment early in the clinical course with fluid hydration, pain control, and "gland rest."
- Historically, gland rest consisted of making a patient "nothing by mouth" with intravenous (IV) fluid support, followed by the slow reintroduction of food.
- When foods are tolerated, carbohydrate-rich foods are introduced first.

■ Patients with a more severe clinical course should receive some form of nutritional support because of the inherently elevated level of stress and hypercatabolism.

■ It is widely accepted that enteral nutrition is preferred over parenteral.

■ Recent studies have shown jejunal feeds in adults are well tolerated by most patients with uncomplicated disease.
- Allows for gut stimulation while preventing gastric and intestinal phases of pancreatic secretion, preserving gland rest.
- Complications, such as persistent vomiting or ileus, may prevent placement of a feeding tube and tolerance of jejunal feeds; enteral nutrition should be first-line therapy when possible.

■ Total parenteral nutrition can be initiated by days 3–5 of illness.
- IV lipids seem to be safe and beneficial, as long as triglyceride levels are monitored closely.

SPECIFIC TREATMENTS

■ Pain control.
- Morphine is often avoided because of its known effects on the sphincter of Oddi, mainly spasm, and the theorized exacerbation of the patient's abdominal pain.
- However, recent evidence does not support opioid avoidance and it is often used clinically.
- Hydromorphone (Dilaudid) and meperidine are commonly used alternatives.
- Meperidine lowers seizure thresholds in susceptible patients and should be used sparingly in such populations.

■ Following supportive therapies, the clinical course directs additional treatment.

- Severe complications (eg, shock, systemic inflammatory responses, sepsis, multiorgan dysfunction) may require
  - Antibiotics
  - Aggressive fluid management
  - Respiratory support
  - Monitoring in intensive care units (ICUs)
- Prognostic systems used to predict clinical severity in adults have not been validated in children.
- Recent studies have attempted to develop a prognostic scoring system for children loosely based on the Ranson criteria.
  - Based on parameters obtained at admission and 48 hours after illness onset.
  - Admission criteria.
    - Age <7 years
    - Weight <23 kg
    - White blood cell count >18,500
    - Lactate dehydrogenase level >2,000
  - 48-hour criteria.
    - Trough calcium <8.3 mg/dL
    - Trough albumin <2.6 mg/dL
    - Fluid sequestration >75 mL/kg per 48 hours
    - Rise in blood urea nitrogen >5 mL/dL
  - Patients were given one point for each criterion met, with scores assessed at admission and 48 hours of illness.
  - Score of zero on admission and during the first hours of illness: lowest probability of developing severe disease; admit to routine ward beds.
  - Scores ≥3 on admission: Admit to ICU for intensive monitoring.
  - Intermediate scores: Admit and closely monitor, with a low threshold for transfer to ICU if scores increased to ≥3.
- Chronic pancreatitis.
  - Although immediate treatments are often supportive (eg, pain control, fluid management, gland rest), identifying the cause assists in determining therapy following stabilization.
  - In adults, several treatment options have been proposed: exogenous pancreatic enzyme supplementation and antioxidant use.
  - Patients often progress to pancreatic exocrine insufficiency.
  - Supplementation of exogenous pancreatic enzymes, although not curative, can help relieve symptoms, prevent morbidity and mortality, and improve quality of life.
  - Oxidative stress has been proposed as a mechanism leading to pancreatic gland destruction in chronic pancreatitis.
    - Antioxidant agents, such as selenium, are decreased in patients with chronic pancreatitis.
  - Because pain control is often a cornerstone of management in pancreatitis, physicians must recognize patients who exhibit drug-seeking tendencies and address any abusive behaviors, or refer to a specialist with more experience in dealing with chronic pain.

WHEN TO ADMIT

- Admit all children suspected of having acute pancreatitis, with initiation of supportive therapy and monitoring.
- Younger, smaller children with elevated white blood cell counts or lactate dehydrogenase may benefit from direct ICU admission and intensive monitoring.
- Children with chronic pancreatitis should be admitted based on severity of clinical symptoms (ie, intractable vomiting, need for IV fluids or nutritional support, inability to tolerate oral pain medications).

WHEN TO REFER

- All patients diagnosed with pancreatitis would likely benefit from an evaluation by a pediatric gastroenterology specialist.
- More severe cases with associated hemorrhagic or necrotic component require surgical consultation for therapeutic peritoneal lavage or pancreatic necrosectomy.
- Patients with pancreatitis and intractable pain may benefit from evaluation by a pain specialist.
- Patients with recurrent pancreatitis and a positive family history may benefit from a genetic evaluation by a specialist to determine the utility of additional genetic testing.

FOLLOW-UP

- Closely monitor patients after discharge from the hospital.
- Children presenting with pancreatitis require follow-up in the primary and specialty care settings.
- Reassess such children for a return to baseline function and activity in the outpatient setting.
  - Pancreatic enzyme elevations may last for days after an acute pancreatitis attack.

- Although no universal guidelines direct follow-up care, repeat laboratory tests to confirm continued decreases in amylase and lipase levels may reassure families and physicians that the disease is resolving.
- In children whose clinical course was more complicated with documented pancreatic fluid collections (pseudocyst), repeat imaging may be indicated.
- Indications for genetic testing should be based on individual patient factors, such as recurrent attacks of pancreatitis or a strong family history.
- Children with chronic pancreatitis or extremely severe acute attacks with pancreatic necrosis may require additional monitoring for pancreatic endocrine and exocrine insufficiency.

COMPLICATIONS

- Several known complications (**Box 2**).
  - Anatomic changes to the pancreatic tissue
  - Gastrointestinal and metabolic dysfunction
  - Systemic complications
  - Pseudocyst development
    - One of the more common complications (≤25% of cases, especially those whose underlying etiology is traumatic)
      - With improved imaging, small pseudocysts are increasingly identified.
      - Most resolve spontaneously, but those that persist and develop a mature capsule must be drained endoscopically, surgically, or percutaneously with radiographic guidance.

Box 2. Complications of Pancreatitis

Pancreatic
- Ascites
- Diabetes mellitus
- Exocrine insufficiency
- Necrotizing pancreatitis
- Pancreatic abscess
- Pancreatic calculi
- Pancreatic carcinoma
- Pancreatic duct strictures
- Pancreatic fibrosis
- Pancreatic fistula
- Pancreatic phlegmon
- Pancreatic pseudocyst

Gastrointestinal/Metabolic
- Biliary obstruction
- Bowel infarction
- Gastritis
- Gastrointestinal fistula
- Hemorrhage
- Hepatic vein thrombosis
- Hepatorenal syndrome
- Hyperglycemia
- Hyperkalemia
- Hypertriglyceridemia
- Hypoalbuminemia
- Hypocalcemia
- Ileus
- Jaundice
- Metabolic acidosis
- Peptic ulcer disease
- Portal vein thrombosis
- Varices—splenic vein

Systemic
- Adult respiratory distress syndrome
- Atelectasis
- Disseminated intravascular coagulation
- Electrocardiographic changes
- Encephalopathy
- Fat emboli
- Fat necrosis
- Hypotension
- Mediastinal abscess
- Pericardial effusion
- Pleural effusion
- Pneumonitis
- Psychosis
- Renal failure
- Renal vessel thrombosis
- Respiratory failure
- Sepsis
- Sudden death
- Thrombosis

- Pay particular concern to the relationship between patients with known hereditary pancreatitis and the development of pancreatic carcinoma.
  - Patients with hereditary pancreatitis have a high risk for pancreatic cancer up to several decades after the initial onset of the pancreatitis.
- Patient counseling and concomitant monitoring are crucial for appropriate management.
- Physician awareness of appreciated complications is important in the ultimate recognition and treatment of an individual patient's clinical course.
- Irreversible damage.
  - Chronic setting: caused by repeated episodes of inflammation
  - Acute setting: caused by necrotic changes
- Evidence of fat malabsorption or insulin insufficiency may be signs of pancreatic gland dysfunction and prompt additional investigations or treatments.

PROGNOSIS

- Acute
  - In most cases, acute pancreatitis in children is a single event with a relatively predictable course and overall benign outcome.
  - Morbidity rates range from 0% to ~80%, depending on study size and specific populations assessed.
- Chronic
  - Prognosis depends on multiple factors.
    - — Underlying cause
    - — Early recognition of increased susceptibility
    - — Family and patient education and understanding
    - — Avoidance of exacerbating factors that contribute to recurrent attacks

PREVENTION

- Acute
  - Prevention is difficult because the cause is often unknown.
  - Improved childhood safety measures, such as booster seats in cars, may prevent injury.
  - Systemic infection and structural abnormalities are more difficult to prevent.
- Chronic
  - In children and adolescents with known chronic pancreatitis, universal preventive measures (ie, avoiding fatty foods, stress, alcohol, and tobacco) may help decrease future events and slow the irreversible damage.

DEFINITION

- Scaly, raised lesions that range in size from small papules (1–3 mm in diameter) to large plaques (>10 cm in diameter).
- The scale can vary from thin desquamation to thick adherence.

SIGNS AND SYMPTOMS

Psoriasis

- The classic psoriasis lesion is a sharply demarcated, erythematous plaque with an overlying silvery scale.
- Plaques are usually symmetric and occur commonly on the elbows and knees.
  - May also occur on the scalp, ears, gluteal cleft, and umbilicus
- Scale removal can produce characteristic pinpoint bleeding (Auspitz sign).
- Inverse psoriasis affects the intertriginous areas, such as the axillae and groin.
  - Appears as smooth, erythematous patches, usually without any scale
- Small, drop-like papules with a silvery scale, called *guttate psoriasis,* commonly occur on the trunk and proximal extremities.
  - Often triggered by streptococcal disease
- Pustular psoriasis is rare in childhood; however, it may be seen during the first week of life.
  - Can become generalized with hundreds to thousands of pustules occurring in areas of erythema and scaling
  - May remain localized to palms and soles or in the folds of the neck and inguinal creases
- Erythrodermic psoriasis characterized by widespread erythema and exfoliation.
- Nail changes can include
  - Pitting
  - Oil spots (yellowish-brown spots signifying separation of the nail from the nail bed)
  - Onycholysis (distal separation of the nail from the nail bed)
  - Occasional destruction of the entire nail
- Linear psoriatic plaques in areas of skin trauma (Koebner phenomenon) can be useful in diagnosis.
- Viral infection, sunburn, and drug eruptions can precipitate the onset of psoriasis.
- Arthritis may precede or follow the development of skin lesions.
  - Most commonly involved joints are the knee and the small joints of the hands and feet.

Pityriasis Rosea

- Classically, a single, oval, erythematous, scaly lesion (herald patch), usually >1 cm in diameter.
  - Develops on the trunk but may be seen anywhere on the body.
  - Appears several days to weeks before the appearance of oval plaques with thin scale in a "Christmas tree" pattern orienting along skin cleavage lines.
- Atypical individual lesions can be vesicular, pustular, or purpuric.
- Mild pruritus may occur with the generalized eruption.
  - Usually resolves within 4–8 weeks but can take up to 6 months
- Recurrence is uncommon.
- Pharyngitis, headache, and malaise may precede appearance of skin lesions, but this is not usual.

Pityriasis Lichenoides

- Characteristic pityriasis lichenoides et varioliformis acuta (PLEVA) lesions are recurrent crops of erythematous papules and papulovesicles 2–4 mm in diameter.
  - Often become pustular, hemorrhagic, or necrotic
- Occur most commonly on the trunk and extremities.
- Usually spares scalp, face, palms, and soles.
- Gradual resolution over weeks to months.
- Post-inflammatory hypopigmentation can occur, especially in darker-skinned children.
- The characteristic lesions are reddish-brown, oval, scaly papules and small, thin plaques that usually occur on the trunk and extremities.
- Lesions may persist for months to several years before resolving without scarring.
- Ulceronecrotic form is a rare variant in which patients have fever and ulceronecrotic plaques.
  - Extensive painful necrosis of the skin with subsequent secondary infection leading to septicemia

Pityriasis Rubra Pilaris

- A combination of characteristic lesions includes
  - Scaly, erythematous macules
  - Reddish-orange keratotic papules
  - Yellow thickening of the palms and soles (keratoderma)
- Unaffected skin or "islands of sparing" can be seen scattered within the erythrodermic skin.

Lichen Planus

- Characteristic lesions are
  - Shiny, flat-topped, violaceous, polygonal papules and plaques
  - From 2–15 mm in diameter
  - Usually appear in a symmetric fashion on the extremities
  - May be seen on the scalp, face, genitalia, palms, and soles
- Lesions on the buccal mucosa and tongue are less common but appear as white, pinpoint papules in a lacy pattern (Wickham striae).
- Rare variations of lichen planus include bullous, linear, hypertrophic, and annular.
- Nail involvement is rare in children but may consist of longitudinal ridging or severe dystrophy.
- Lesions may develop in a linear array at the site of skin trauma (Koebner phenomenon).
- Pruritus can be severe.

Lichen Nitidus

- Characteristic lesions are flesh-colored to white, flat-topped papules 1–2 mm in diameter.
- Can occur anywhere on the body but usually seen in clusters on the trunk.
- Pruritus may or may not occur.
- A useful diagnostic finding is the presence of a linear group of papules within an area of skin trauma (Koebner phenomenon).

Lichen Striatus

- Characteristic lesions are flesh-colored or erythematous papules 1–2 mm in diameter that can coalesce into a plaque.
- Most commonly on a single extremity in a linear distribution, following Blaschko lines.
  - May be seen on the abdomen and face
- If a lesion extends to a finger or toe, nail dystrophy may occur.
- Diagnosis is clinical, and skin biopsy is rarely necessary.
- Lesions resolve spontaneously and do not require treatment.

DIAGNOSTIC APPROACH

- Psoriasis: Diagnosis is usually clinical; skin biopsy can be confirmatory.
- Pityriasis rosea: Diagnosis is usually clinical; skin biopsy can be confirmatory.
- PLEVA and pityriasis lichenoides chronica: Diagnosis is sometimes difficult to make clinically, and a skin biopsy can be confirmatory.
- Pityriasis rubra pilaris: Biopsy can be confirmatory.
- Lichen planus: Diagnosis is clinical; skin biopsy if diagnosis is uncertain.

CLASSIFICATION

Pityriasis Rubra Pilaris

- A clinical classification of 5 types has been proposed.
  - Type I: classical type with adult onset.
  - Type II: atypical type with adult onset.
  - Type III: classical type with juvenile onset (10% of cases).
  - Type IV: circumscribed type with juvenile onset (25% of cases).
  - Type V: atypical type with juvenile onset, usually hereditary (5% of cases).
  - A sixth, HIV-associated, type has been proposed but is controversial.
- Types III and IV usually occur before puberty; type V is usually present at birth or occurs in the first few years after birth.
- In type III, macules and papules coalesce into patches and plaques that spread from the head to the trunk and extremities over weeks to months.
- In type IV, the usual lesions are erythematous plaques on the elbows and knees.
- Hyperkeratosis (scaly skin) with scant erythema along with keratoderma (thickened skin) of the palms and soles characterize type V.
- Keratoderma can occur in each of the types.

SPECIFIC TREATMENTS

Psoriasis

- No cure for psoriasis exists; effective treatment is available to control the disorder.
- Natural history includes remissions and exacerbations.
- Medium potency topical corticosteroids with or without topical vitamin D (calcipotriene) can often control the condition.
  - High- or super-potency topical corticosteroids may be necessary if new lesions develop.
- Coal tar preparations may be effective, but many patients do not like to use them because of cosmetic issues, including staining of clothes.
- Other treatment modalities include
  - UV-B phototherapy
  - Methotrexate
  - Biologic agents, such as etanercept (tumor necrosis factor-α inhibitor) and ustekinumab (interleukin 12 and interleukin 23 antagonist)

- Etanercept can be effective in the treatment of moderate to severe plaque psoriasis in children and adolescents.
- Oral retinoids can be effective in the treatment of generalized pustular psoriasis and erythroderma.
- Systemic corticosteroids should be avoided because they can exacerbate the disease and can cause erythroderma following discontinuation.

Pityriasis Rosea

- Self-limited; most children do not require any treatment.
- Pruritus can be managed with emollients or oral antihistamines.
- Sunlight or UV-B phototherapy can hasten resolution of lesions.
- In one study, oral erythromycin was effective.

Pityriasis Lichenoides

- Lesions may resolve without treatment; however, emollients, oral antihistamines, and topical corticosteroids may alleviate pruritus.
- Oral erythromycin or UV-B phototherapy seems to hasten resolution.
- Methotrexate and systemic corticosteroids are often used in cases of the febrile ulceronecrotic form.

Pityriasis Rubra Pilaris

- Spontaneous resolution of types III and IV may occur, but type V continues throughout life.
- With mild forms of types III and IV, emollients may relieve skin dryness, while keratolytics (lactic, salicylic, or glycolic acid–based products) may soften and decrease skin thickening.
- Topical corticosteroids can help relieve pruritus.
- Topical retinoids, although not curative, can help to smooth papules.
- Complete clearance of type IV pityriasis rubra pilaris with topical tazarotene (retinoid) was recently reported.
- Oral retinoids are often used for severe type III and type V.

Lichen Planus

- Medium- to high-potency topical corticosteroids, to aid control of pruritus and resolution of lesions.
- Oral antihistamines are effective in relief of pruritus.
- Topical corticosteroids in gel or solution form can relieve pain in oral erosions and ulcerations.
- Remission often occurs ≤6 months.
  - Some cases can take up to 2 years for resolution.
  - Oral involvement may take as long as 5 years to resolve.
- Systemic corticosteroids are useful in children with extensive or unresponsive lesions.

Lichen Nitidus

- Lesions resolve spontaneously over months to years.
- Because many children are asymptomatic and the lesions resolve spontaneously, no treatment is necessary.
- Emollients, oral antihistamines, and topical corticosteroids may relieve pruritus.

DEFINITION

- Infection with any of a variety of parasites, including protozoa and helminths (nematodes, trematodes, and cestodes)

SIGNS AND SYMPTOMS

Protozoal Infections

Amebiasis

- 90% of *Entamoeba histolytica* infections are asymptomatic.
- Intestinal amebiasis has a subacute onset, usually over 1–3 weeks.
- Symptoms range from mild diarrhea to severe dysentery, producing abdominal pain, diarrhea, and bloody stools.
- Weight loss in nearly 50% of patients.
- Fever in 8%–38% of patients.
- Fulminant colitis with bowel necrosis leading to perforation and peritonitis is rare but is associated with a mortality rate >40%.
- Amoebic liver abscess.
  - Most common extraintestinal manifestation of amebiasis.
    - Less common in children than in adults
  - Symptoms usually appear within 8–20 weeks (in travelers, 5 months after return from endemic area in 95% of patients); longer intervals have been reported.
    - Pain in the right upper quadrant
    - Fever
    - Anorexia
    - Fatigue
    - Diarrhea (in less than one-third of patients)
    - Jaundice (uncommon)

Amoebic Meningoencephalitis

- Primary amebic meningoencephalitis (PAM)
  - Bifrontal headaches unresponsive to analgesics
  - Fever (temperature 38.0°C–41.0°C [100.4°F–105.8°F])
  - Alteration in taste or smell, and/or rhinitis, may be noted early.
  - Emesis
  - Seizures
  - Lethargy
  - Nuchal rigidity
  - Cerebellar ataxia
  - Dysfunction of the third, fourth, and sixth cranial nerves
- Granulomatous amoebic encephalitis (GAE)
  - Disease of immunocompromised and debilitated individuals; chronic and insidious
  - Hemiparesis
  - Personality changes
  - Seizures
  - Neck stiffness
  - Headaches
  - Fever
  - Sinusitis
  - Otitis media
  - Cutaneous lesions
  - Corneal ulcers

Cryptosporidiosis

- Varies from asymptomatic infection to severe enteritis and fatal dehydration
- Acute diarrhea (frequent, watery, foul-smelling, non-bloody stools)
  - Resolves spontaneously in 1–20 days.
  - Occasionally, healthy infants may develop chronic and persistent diarrhea, leading to malnutrition and growth retardation.
- Malaise
- Nausea
- Anorexia
- Fatigue
- Abdominal cramps
- Weight loss
- Fever
- Vomiting
- Clinical manifestations of cryptosporidiosis in patients with AIDS include
  - Cholecystitis
  - Cholangitis
  - Hepatitis
  - Pancreatitis
  - Respiratory cryptosporidiosis is seen mainly in patients with AIDS; symptoms include
    - Cough
    - Dyspnea
    - Fever
    - Expectoration
    - Chest pain
  - Biliary cryptosporidiosis is seen exclusively in patients with AIDS; symptoms include
    - Right upper quadrant pain
    - Fever
    - Nausea and vomiting with or without diarrhea

Toxoplasmosis

- Congenital disease
  - Most (70%–90%) congenitally infected neonates are asymptomatic.

- Clinical manifestations at birth include
  - Hepatosplenomegaly
  - Lymphadenopathy
  - Hydrocephalus and intracranial calcifications
  - Seizures and neurologic deficits
  - Chorioretinitis
  - Rash
  - Jaundice
- Acquired disease
  - Usually asymptomatic
  - Cervical lymphadenopathy
  - Fever
  - Myalgia
  - Fatigue
  - In some, infectious mononucleosis–like manifestations
    - Sore throat
    - Fever
    - Malaise
    - Adenopathy
    - Splenomegaly
    - Rash
- Disease in immunodeficient patients
  - Localized infections
    - Encephalitis
    - Meningoencephalitis
      - Fever
      - Headache
      - Deterioration in mental status
      - Seizures
      - Hemiparesis
      - Abnormal speech
    - Pneumonitis
    - Myocarditis
    - Pericarditis
    - Hepatitis
- Ocular disease/chorioretinitis
  - Bilateral in congenital form and unilateral in acquired form
  - Nystagmus
  - Blurred vision
  - Photophobia
  - Central vision loss

Malaria

- Symptoms occur
  - Every second day with *Plasmodium falciparum, Plasmodium vivax,* and *Plasmodium ovale.*
  - Every third day with *Plasmodium malariae.*
  - These classic patterns are rarely observed.
- Combination of influenza-like symptoms
  - Fever
  - Chills
  - Sweats
  - Headaches
  - Nausea and vomiting
  - Body aches
  - General malaise
  - Anemia
  - Enlarged spleen
- Severe malaria
  - Signs of organ dysfunction
  - High *P falciparum* parasite density (>10%)
  - Cerebral malaria
    - Abnormal behavior
    - Impairment of consciousness
    - Seizures
    - Coma
    - Other neurologic abnormalities
  - Severe anemia
  - Pulmonary edema
  - Acute respiratory distress syndrome
- Congenital malaria
  - Fever
  - Severe anemia
  - Hepatosplenomegaly

Babesiosis

- Gradual onset of malaise, fatigue, and anorexia.
- Followed by fever with
  - Chills
  - Sweats
  - Myalgia
  - Headache
  - Vomiting
- Less commonly
  - Conjunctival injection
  - Meningismus
  - Altered sensorium
  - Nonproductive cough
- Symptoms may last for several weeks or sometimes months.
- Infection with *Babesia divergens* is associated with fulminant illness.
- In immunodeficient patients
  - Hemolytic anemia
  - Jaundice
  - Dark urine

Nematode Infections

Trichinellosis

- 1–7 days after infection
  - Asymptomatic or gastrointestinal symptoms
    - Nausea
    - Vomiting
    - Diarrhea
    - Constipation
    - Abdominal pain
- Muscle stage (lasts ≥1–5 weeks)
  - Myalgia; may mimic rheumatic pain
  - Eyelid edema
  - Eosinophilia
  - High and prolonged fever
  - Weakness
  - Malaise
  - Headache
  - Subconjunctival hemorrhages, retinal hemorrhages
  - Splinter hemorrhages under fingernails
  - Facial flushing
  - Urticarial or macular rashes
  - Hoarseness
  - Dyspnea
  - Dysphagia

Hookworm Infections

- Symptoms and signs correlate with the stage of infection.
- Early findings.
  - Itching.
  - Focal eruptions with or without edema.
  - Enlargement of adjacent lymph nodes (ground itch).
  - Mild respiratory symptoms, cough.
  - If severe, Löffler syndrome may develop.
- Intestinal phase.
  - Abdominal pain
  - Nausea
  - Vomiting
  - Increased flatulence
  - Diarrhea
  - Constipation
  - Symptoms of anemia
- Chronic infection.
  - Anemia

Ascariasis

- Usually asymptomatic.
- Löffler syndrome (acute transient pneumonitis) occurs 1–2 weeks after ingestion of the eggs.
  - Fever
  - Eosinophilia
  - Urticaria
  - Abdominal discomfort
  - Nausea
  - Vomiting
  - Diarrhea
  - Malnutrition
  - Intestinal obstruction
- Worm migration into the biliary tree.
  - Biliary colic
  - Cholecystitis
  - Ascending cholangitis
  - Biliary strictures and hepatic abscesses
  - Pancreatitis
  - Appendicitis
- Migration may occur through body orifices, such as the mouth, nose, anus, and lacrimal duct.

Toxocariasis

- Most patients who are mildly infected are asymptomatic.
- Symptomatic children with toxocariasis usually present with
  - Fever
  - Leukocytosis with eosinophilia
  - Hypergammaglobulinemia
  - Hepatomegaly
  - Splenomegaly and lymphadenopathy
- Possible allergic manifestations include
  - Urticaria
  - Rhinorrhea
  - Asthma/wheezing
- Constitutional symptoms include
  - Anorexia
  - Weakness
  - Failure to gain weight
  - Myalgia
  - Arthralgia
  - Nocturnal sweats
- Neurologic symptoms are less frequent.
  - Irritability
  - Seizures
- Myocarditis.
- Congestive heart failure.
- Pleural effusion.
- Eosinophilic ascites.

- Meningoencephalitis.
- Ocular involvement, usually without other systemic involvement.
  - Unilateral solitary posterior retinal lesion.
  - Granulomatous mass or multiple lesions may be seen.
  - Lesions are painless; some are asymptomatic and are found incidentally on routine retinal examination.
  - Strabismus.
  - Visual impairment.
  - Unilateral loss of vision.
  - Leukocoria.

Cestode Infections

Taeniasis

- Often asymptomatic
  - Main symptom is intermittent passage of the proglottids, either with the stool or spontaneously.
  - Nausea, diarrhea, and abdominal pain or discomfort.

Cysticercosis

- The most common initial manifestation of neurocysticercosis is a seizure.
- Cysticercal encephalitis.
  - Fever
  - Headache
  - Vomiting
  - Impaired consciousness
  - Reduced visual acuity
  - Seizures
- Possible extraneural cysticercosis.
  - Small palpable nodules that may become inflamed
  - Muscle pain

Hymenolepiasis

- Usually asymptomatic
- Symptoms of heavy infection
  - Abdominal pain
  - Nausea
  - Vomiting
  - Diarrhea
  - Anorexia
  - Weakness
  - Irritability
  - Headache

DIAGNOSTIC APPROACH

Protozoal Infections

Amebiasis

- Microscopic examination of stool (Up to 3 may be sent.)
- Liver amoebic abscesses are usually diagnosed on the basis of
  - Clinical presentation
  - Recognition of epidemiologic risk factors
  - Serologic testing
  - Noninvasive imaging studies

Amoebic Meningoencephalitis

- Infections caused by the free-living amoebae are difficult to diagnose, and most are recognized on autopsy or necropsy.
- PAM.
  - Neuroimaging studies may be normal early in disease but may show signs of increased intracranial pressure later.
  - Laboratory studies (including cerebrospinal fluid [CSF] examination and wet mount).
- GAE.
  - Neuroimaging
  - CSF examination
  - Corneal scrapings to look for cysts, and culture

Cryptosporidiosis

- Antigen testing
- Microscopic examination of stool, aspirated fluid, or tissue samples

Toxoplasmosis

- If suspected, patient should undergo complete clinical evaluation, including ophthalmologic, neurologic, and auditory examination (see Laboratory Findings and Imaging sections).
- After delivery, neonates should be evaluated for congenital toxoplasmosis if
  - The mother had a primary infection *or*
  - The mother has HIV infection and serology suggestive of past infection.
- In patients with ocular involvement, diagnosis is based on classic eye findings and serologic testing.
- Clinical and laboratory data should be carefully correlated during patient evaluation and management.
- In some states, testing of newborns is done as part of newborn screening; those with positive screen results should be assessed completely for evidence of infection.

Malaria

- Most commonly used diagnostic tools.
  - Microscopic diagnosis
    - Thick smears are more sensitive but cannot be used to differentiate among species.
    - Inexperienced microscopists may find identification of parasites easier with thin smears.
  - Rapid diagnostic tests based on immunochromatographic techniques
- Diagnosis can be difficult in non-endemic areas.
  - Health care professionals are not familiar with the disease.
  - Laboratorians inexperienced with malaria may fail to detect parasites in blood smears.

Babesiosis

- Diagnosis is made by demonstrating the organism in blood smears.

Nematode Infections

Trichinellosis

- The diagnosis should be suspected in patients with
  - Suggestive clinical history (consumption of inadequately cooked meat, particularly pork)
  - Eosinophilia
- The presence of symptoms in other patients who ate the same food makes the diagnosis stronger.
- Serologic testing.

Hookworm Infections

- Diagnosed by identifying eggs in stools
  - Stool smears are often negative in early stages of infection.

Ascariasis

- Presence of worms.
- Diagnosis is made by demonstrating characteristic eggs in stools by direct microscopy.
  - Eggs may not appear in the stools until at least ≥40 days of infection.
- Imaging studies may demonstrate worms if there is
  - Intestinal obstruction
  - Hepatobiliary or pancreatic ascariasis
- Serologic testing is not helpful.

Toxocariasis

- Definitive diagnosis requires demonstration of larvae in tissue sections, but this is rarely needed.
- Diagnosis is usually based on clinical findings and serologic testing.

Cestode Infections

Taeniasis

- Diagnosis is made by microscopic identification of eggs or proglottids in stool.
  - May not be possible during the first 3 months of infection

Cysticercosis

- Definitive diagnosis is made by demonstrating the cysticercus in the involved tissue.
- Demonstration of eggs or proglottids in stool specimen may support but not prove the diagnosis.
- For neurocysticercosis, magnetic resonance imaging (MRI) and computed tomography (CT) are the most reliable imaging techniques.
- Serologic testing.

Hymenolepiasis

- Diagnosis is made by demonstrating eggs in stool specimens.

LABORATORY FINDINGS

Protozoal Infections

Amebiasis

- Serologic testing specific to
  - *E histolytica.*
  - 10%–35% of uninfected individuals in endemic areas have antiamebic antibodies related to previous, often undiagnosed, infection with *E histolytica.*
    - Negative serologic test results in these populations help exclude disease.
    - Positive serologic test results do not distinguish between acute infection and past exposure.
- Fecal and serum antigen detection assays.
  - Quick and easy
  - Able to differentiate among strains
  - Greater sensitivity than microscopy
  - Potential for early diagnosis during infection and in endemic areas where serologic testing is less useful
- Polymerase chain reaction (PCR) techniques can detect *E histolytica* in stool specimens.
  - PCR-based techniques are the most sensitive and specific methods.
    - Not widely available

Amoebic Meningoencephalitis

- PAM
  - Increased leukocyte count.
  - Hyperglycemia.
  - Glycosuria.
  - CSF examination.
    - Pleocytosis with polymorphonuclear neutrophil predominance.
    - Increased CSF protein.
    - Normal or decreased glucose.
    - Motile amoebae may be seen on wet mount; preferably, use unrefrigerated CSF collected ≤30 minutes of the evaluation.
  - Performing culture on non-nutrient agar plated with *Escherichia coli* is the definitive way to diagnose.
- GAE
  - Diagnosis is made by finding amoebae in tissue sections
    - Stained with hematoxylin and eosin *or*
    - Indirect immunofluorescence using rabbit anti-amoebae serum samples
  - Cysts of infecting amoebae can be recognized in corneal scrapings that have been stained with Calcofluor-white.
  - *Acanthamoeba* can also be grown on bacterial culture in non-nutrient agar with bacteria for identification.

Cryptosporidiosis

- Modified Kinyoun acid-fast stain of ≥3 stool samples.
  - Stool samples are usually concentrated by the sucrose flotation or the formalin acetate method.
- Immunofluorescent staining that uses monoclonal antibodies and enzyme-linked immunosorbent assay (ELISA) kits can be used to detect oocysts in stool and tissue specimens.

Toxoplasmosis

- The most definite test for diagnosis of toxoplasmosis is isolation of the organism from infected tissue or body fluids by inoculation into laboratory animals or by tissue culture.
  - These techniques are not routinely available.
- The primary method used currently is based on detecting specific antibodies and monitoring immune response.
- Molecular methods involving PCR for detecting *Toxoplasma* DNA in tissue and fluid samples have been developed.
- ELISA.
  - Serum immunoglobulin G (IgG) usually becomes positive 4–8 weeks after infection.
    - Remains positive indefinitely
  - Paired serum samples should be tested simultaneously 3 weeks apart to document an increase in titers of ≥4-fold.
  - Serum IgM levels should be tested simultaneously with IgG.
  - ELISA IgM tests are more sensitive than the indirect immunofluorescence antibody test.
    - IgM test may remain positive for 6 months, and false-positive results can occur.
  - Testing is complex in newborns; serum from mother and neonate should be tested simultaneously.
    - Serum levels of IgA and IgE for *Toxoplasma* can be tested.
    - These become negative sooner than IgM, giving more precise information about timing of infection.
    - Anti-*Toxoplasma* IgA and IgE tests are available only at *Toxoplasma* referral laboratories.
- Definitive diagnosis of congenital toxoplasmosis during pregnancy can be made by amniotic fluid sampling.
  - *Toxoplasma* in amniotic fluid with DNA PCR or tissue culture or mouse inoculation is considered diagnostic.
  - Fetal blood sampling may be used to isolate *Toxoplasma* from fetal leukocytes and test for IgM antibody.
- In infant with suspected toxoplasmosis
  - Diagnosis is confirmed serologically by demonstrating
    - Positive IgM or IgA
    - Higher infant IgG titer than the mother *or*
    - Persistently positive IgG >1 year
  - CSF should be analyzed for cells, protein, glucose, and *Toxoplasma* antibodies with PCR.
  - Serum samples should be evaluated for IgG, IgM, IgA, and IgE antibodies for *Toxoplasma.*
- Diagnosis of toxoplasmosis in older children and adults who are immunocompetent relies on presence of a positive IgM titer or a 4-fold increase in IgG titers after 3 weeks.
- Classic histopathologic findings in tissue samples, such as lymph nodes, strongly support the diagnosis.
  - Histologic identification of proliferating organisms is definitive.

- Culture-isolated *Toxoplasma* in tissue or body fluid samples or identification of nucleic acid material with DNA PCR is definitive.
- In immunocompromised patients, including those with HIV infection, interpretation of serologic testing is complex.
- Ocular disease.
  - Examination of the vitreous fluid or aqueous humor on DNA PCR may be needed if retinal lesions are atypical or patient fails to respond to antimicrobial therapy.

Malaria

- Peripheral blood smears.
- Rapid diagnostic tests.
- Serologic testing (indirect immunofluorescence or ELISA) does not detect current infection.

Babesiosis

- Diagnosis is made by demonstrating the organism in thick and thin smears prepared for Wright and Giemsa stains.
  - Cluster of 4 small merozoites ("tetrads") in erythrocytes.
  - Multiple parasites may be present in a single cell.
  - Occasionally 3 chromatin dots in a single parasite.
- Serologic testing if blood smears are nondiagnostic.
  - Indirect immunofluorescent assay (available in reference laboratories)
- PCR is more sensitive than blood smear.

Nematode Infections

Trichinellosis

- Serologic tests.
  - ELISA (most sensitive).
  - Indirect fluorescent antibody test.
  - Latex agglutination.
  - Serologic tests are helpful only after the second week of infection.
  - Testing of paired acute and convalescent serum is diagnostic.
  - Eosinophilia usually appears during second week of the muscle phase and can be as high as 70%.
  - Creatine kinase and lactate dehydrogenase concentrations may be elevated.
  - Ig levels may be high.
- Larvae found microscopically in muscle biopsy samples is definitive.
  - Only occurs after first 2 weeks after ingestion

Hookworm Infections

- Stool concentration techniques may be needed if infection is mild.
  - Repeat stool examinations may also be needed.
- Species can be identified by PCR.

Ascariasis

- A single stool sample usually is sufficient.
- Adult worms are sometimes passed in stool and provide a clue to diagnosis.
- Eosinophils and, occasionally, *Ascaris* larvae may be demonstrated in sputum samples.

Toxocariasis

- Serologic testing to confirm diagnosis.
  - ELISA is most frequently used, with high sensitivity and specificity.
  - Western blot and immunofluorescence tests are also used.
- Total leukocyte count may be as high as 30,000 cells/mcL (30×10^9/L), with ≤80% eosinophils.
- Hypergammaglobulinemia with high IgE levels.
  - Sometimes 10–15× normal levels
- Elevated isohemagglutinins to A and B blood groups.
- During the pulmonary phase, eosinophils may be detected in respiratory secretions.
- With central nervous system (CNS) involvement, CSF specimens may show eosinophils.

Cestode Infections

Taeniasis

- Eggs are microscopically indistinguishable from those of other tapeworm species, especially *Echinococcus.*
- Species can be determined by microscopic examination of the gravid proglottids and scolex, if available.

Cysticercosis

- Serologic test of choice is the Centers for Disease Control and Prevention (CDC) immunoblot assay with purified *Taenia solium* antigens.
  - 100% specificity
  - 50%–97% sensitivity
- Enzyme immunoassay.
  - Lower sensitivity and specificity
  - Can cross-react with other helminthic infections, such as echinococcosis and filariasis

Hymenolepiasis

- Eggs are apparent in stool specimens.
  - Detection of light infection may require a concentration technique and repeated examination.
- Peripheral blood eosinophilia may be present.

IMAGING

- Amoebic meningoencephalitis
  - PAM
    - Neuroimaging studies may be normal early in the disease but may show signs of increased intracranial pressure later.
    - Meningeal enhancement of the basilar region is frequently reported.
    - Severe brain edema is a late finding that indicates poor outcome.
  - GAE
    - Neuroimaging may reveal space-occupying lesions resembling abscesses, tumors, or hemorrhagic infarction.
- Toxoplasmosis
  - In congenital toxoplasmosis
    - CT of the brain to rule out brain calcification or hydrocephalus
  - To detect congenital toxoplasmosis during pregnancy
    - Serial ultrasonography to assess brain ventricular size or other signs of infection
- Ascariasis
  - Imaging may demonstrate worms if there is
    - Intestinal obstruction
    - Hepatobiliary or pancreatic ascariasis
- Cysticercosis
  - MRI
    - Good visualization of ocular, ventricular, and subarachnoid cysts
    - Demonstrates degree of edema and inflammation, as well as viability of the cysticercus
  - CT
    - Better than MRI for detection of granuloma or calcification

DIAGNOSTIC PROCEDURES

- Trichinellosis
  - Muscle biopsy.
    - Number of larvae per gram of muscle has been used as a guide to severity of infection.
    - Specimens should be
      - Fresh and compressed between 2 microscope slides *or*
      - Digested by artificial gastric juice to increase yield
  - PCR testing to detect *Trichinella*-specific DNA in muscle biopsy specimens is used but availability is limited.

TREATMENT APPROACH

- Amebiasis
  - Amoebae other than *E histolytica* do not require treatment.
  - Treatment for symptomatic disease should be followed by a luminal agent to treat intraluminal infection.
  - A luminal agent alone should be used to treat asymptomatic infection.
- Amoebic meningoencephalitis
  - Treatment should be in centers where neurologic, neurosurgical, and infectious disease experts are available.
  - Consultation with the CDC is advisable.
- Cryptosporidiosis
  - In immunocompetent patients, supportive care, including hydration and nutritional support, may be adequate.
  - Antimicrobial therapy is indicated in severe infection and immunocompromised patients.
- Toxoplasmosis
  - Treatment is not indicated in immunocompetent patients unless clinical symptoms are severe or complications occur.
  - Immunocompromised patients with acute HIV infection or AIDS should be treated even if asymptomatic.
  - Infected pregnant women and neonates, whether symptomatic or not, should be treated as soon as diagnosed.
  - Patients with chorioretinitis are treated when symptoms are present or progressive.
- Malaria
  - Malaria must be recognized promptly to treat the patient in time and to prevent complications.
  - Malaria is a nationally notifiable disease.
    - All cases should be reported to the state health department, which forwards information to the CDC.
  - 3 main factors should be considered.
    - Infecting *Plasmodium* species
    - Clinical status of patient
    - Drug susceptibility of the infecting parasites, determined by geographic area where infection was acquired
  - If malaria is suspected and cannot be confirmed, or if diagnosis is confirmed but species determination is not possible, antimalarial treatment effective against *P falciparum* should be selected.

- Toxocariasis
  - Treatment is recommended for patients with symptoms and those with systemic forms of the disease.
- Cysticercosis
  - Appropriate management depends on
    - Location of cyst
      - For neurocysticercosis, treatment is not generally recommended for an asymptomatic patient with a nonviable single parenchymal cyst that is evidently destroyed by the host immune response; the mainstay of treatment may be anticonvulsants.
    - Viability of cyst
      - In children with viable cysticercus with minimal or no surrounding inflammatory response, cysticidal agent should be given to prevent further perilesional damage and to reduce the risk of developing chronic seizures.
    - Host immune response
    - Presence or absence of symptoms

SPECIFIC TREATMENTS

Protozoal Infections

Amebiasis

- Antibiotic therapy with metronidazole (35–50 mg/kg/d divided in 3 doses orally for 10 days, maximum 750 mg 3 times daily).
- Followed by an intraluminal agent to target the cyst stage.
  - Iodoquinol (30 mg/kg/d divided in 3 doses for 20 days)
  - Paromomycin (25–35 mg/kg/d in 3 divided doses for 7 days)
  - Diloxanide furoate (20 mg/kg/d in 3 doses orally for 10 days)
- Asymptomatic *E histolytica* should be treated with an intraluminal agent.
  - Potential risk of invasive disease and risk of spread to household members

Amoebic Meningoencephalitis

- PAM.
  - Intravenous (IV), or sometimes intrathecal, amphotericin B
- GAE.
  - For encephalitides caused by *Acanthamoeba,* no optimal antimicrobial therapy exists.
- Multiple drugs have been used in PAM and GAE infections with varying degrees of success.
  - Amphotericin B
  - Azithromycin
  - Fluconazole
  - Flucytosine
  - Pentamidine isethionate
  - Sulfa drugs
- Amoebic keratitis.
  - Drugs of choice
    - Chlorhexidine gluconate (component of germicidal soaps)
    - Polyhexamethylene biguanide (disinfectant and swimming pool cleaner)

Cryptosporidiosis

- Nitazoxanide.
  - Treatment for children ≥1 year
  - Treatment for adults with diarrhea caused by cryptosporidiosis or giardiasis
- Paromomycin.
  - Has been used in HIV-infected patients with or without azithromycin
    - Immune therapy (eg, oral administration of human immune globulin, hyperimmune bovine colostrum, and bovine transfer factor) has demonstrated some benefit.
    - Total parenteral nutrition may be needed in HIV-infected patients with chronic diarrhea and weight loss.
- Fluid and electrolyte management of affected patients is essential.
- Nutritional supplements containing medium-chain triglycerides may be helpful.
- Milk and dairy products should be avoided.

Toxoplasmosis

- Pyrimethamine-sulfadiazine
  - Lifelong daily maintenance therapy is needed in patients with AIDS.
  - Pyrimethamine dose in children: 2 mg/kg/d for 3 days, and then 1 mg/kg/d, to a maximum daily dose of 25 mg given for 4 weeks.
  - Sulfadiazine dose: 85–100 mg/kg/d divided every 6 hours for 3–6 weeks.
  - Supplemental leucovorin (folinic acid) to prevent bone marrow toxic effects.
  - For congenital toxoplasmosis, pyrimethamine and sulfadiazine (with folinic acid supplements) should be continued for a prolonged period, often for 1 year.

- Clindamycin and pyrimethamine
  - For patients who are allergic to sulfa drugs
- Ocular toxoplasmosis
  - Corticosteroids provided in addition to pyrimethamine and sulfadiazine
- Patients with CNS disease
  - Corticosteroids provided in addition to pyrimethamine and sulfadiazine in selected patients

Malaria

UNCOMPLICATED (NON-SEVERE) MALARIA

- **Table 1** describes chemotherapy for uncomplicated cases.

SEVERE MALARIA

- Parenteral administration of quinidine gluconate, with continuous infusion until
  - The patient can take oral medication *and*
  - Parasite density is <1%.
- IV artesunate (available through the CDC) if quinidine is unavailable, not tolerated, or patient continues to worsen.
- Quinidine therapy should be combined with doxycycline, tetracycline, or clindamycin.
- Monitor patient closely in an intensive care unit.
- Consult the CDC about treatment of severe cases.

ARTEMISININ DERIVATIVES

- Artemisinin derivatives, such as artemether and artesunate, are used globally in combination regimens to treat malaria and can be administered orally, parenterally, or rectally.
- Oral artemether/lumefantrine is active against chloroquine-resistant *P falciparum* and is approved by the US Food and Drug Administration (FDA) for treatment of acute uncomplicated falciparum malaria.

SUPPORTIVE MEASURES TO OPTIMIZE TREATMENT

- Closely monitor fluid and electrolytes status.
- Treat convulsions with phenobarbital or diazepam.
- Be vigilant about hypoglycemia.
- Correct anemia with packed red blood cell transfusions.
  - Exchange transfusion is controversial; consult expert advice or CDC.

SELF-TREATMENT

- Self-treatment course of artemether-lumefantrine or atovaquone-proguanil (if the individual is not taking this for prophylaxis) can be provided to travelers who are able to determine when it is appropriate to begin treatment and proceed to a source of medical care.
- Advise travelers that self-treatment is not considered a replacement for seeking prompt medical help; travelers should begin treatment while proceeding to medical care.

Babesiosis

- Clindamycin plus oral quinine or atovaquone plus azithromycin for 7–10 days for treatment of symptomatic infection
- Exchange transfusion
  - Consider in fulminant cases with severe hemolysis and high-grade parasitemia (>10%).

Nematode Infections

Trichinellosis

- Mebendazole and albendazole have comparable efficacy.
  - Mebendazole: 200–400 mg 3 times a day for 3 days, and then 400–500 mg 3 times a day for 10 days.
  - Albendazole.
    - — May achieve higher tissue levels.
    - — Dose is 400 mg twice daily for 10–15 days.
  - Both drugs are ineffective for larvae in the muscles.
- Coadministration of steroids (eg, prednisone).
  - Indicated in severe cases, especially with cardiac and CNS involvement
- People who have recently ingested *Trichinella*-contaminated meat should be treated with mebendazole or albendazole.

Hookworm Infections

- May need to correct malnutrition and anemia, including iron supplementation.
- Drugs of choice.
  - Albendazole
    - — Not approved by FDA for treatment of hookworm infections
    - — 400 mg once
  - Mebendazole
    - — No longer available in the United States
    - — 100 mg twice daily for 3 days or 500 mg once
  - Pyrantel pamoate
  - 11 mg/kg (maximum 1 g) for 3 days
- If given to children <2 years, doses of mebendazole and albendazole may be reduced by half.
- Repeat stool examination is recommended 2 weeks after treatment.
- If positive result, retreatment should be considered.
- 3-day course of nitazoxanide may be effective in treating hookworms, but no comparative data with albendazole are available.

Table 1. Chemotherapy of Uncomplicated Malaria

Drug	Dosage
All *Plasmodium* Species Except Chloroquine-Resistant Species[a] (If species is not known, assume chloroquine resistance.)	
Oral drugs of choice	
Chloroquine phosphate	10 mg base/kg (max 600 mg base), then 5 mg base/kg 6 h later, then 5 mg base/kg at 24 and 48 h
OR	
Hydroxychloroquine	10 mg base/kg (max 620 mg base), then 5 mg base/kg 6 h later, then 5 mg base/kg at 24 and 48 h
***Plasmodium falciparum* Acquired in Areas of Chloroquine Resistance (If species is not known, assume chloroquine resistance.)**	
Oral drugs of choice	
Atovaquone/proguanil	<5 kg: not indicated 5–8 kg: 2 pediatric tablets once/d × 3 d 9–10 kg: 3 pediatric tablets once/d × 3 d 11–20 kg: 1 adult tablet once/d × 3 d 21–30 kg: 2 adult tablets once/d × 3 d 31–40 kg: 3 adult tablets once/d × 3 d >40 kg: 4 adult tablets once/d × 3 d
OR	
Artemether/lumefantrine[b]	6 doses over 3 days: 0, 8, 24, 36, 48, and 60 h 5–15 kg: 1 tablet/dose ≥15–25 kg: 2 tablets/dose ≥25–35 kg: 3 tablets/dose ≥35 kg: 4 tablets/dose
OR	
Quinine sulfate	30 mg/kg/d in 3 doses × 3–7 d
PLUS	
Doxycycline	4.4 mg/kg/d in 2 doses × 7 d
OR	
Quinine sulfate	30 mg/kg/d in 3 doses × 3–7 d
PLUS	
Tetracycline	25 mg/kg/d in 4 doses × 7 d
OR	
Quinine sulfate	30 mg/kg/d in 3 doses × 3–7 d
PLUS	
Clindamycin	20 mg/kg/d in 3 doses × 7 d

Table 1 (*continued*)

Drug	Dosage
Alternative	
Mefloquine	15 mg/kg followed 12 h later by 10 mg/kg
***Plasmodium vivax* Acquired in Areas of Chloroquine Resistance (Indonesia or Papua New Guinea)**	
Oral drugs of choice	
Quinine sulfate	30 mg/kg/d in 3 doses × 3–7 d
PLUS	
Doxycycline	4.4 mg/kg/d in 2 doses × 7 d
OR	
Quinine sulfate	30 mg/kg/d in 3 doses × 3–7 d
PLUS	
Tetracycline	25 mg/kg/d in 4 doses × 7 d
Atovaquone/proguanil	<5 kg: not indicated 5–8 kg: 2 pediatric tablets once/d × 3 d 9–10 kg: 3 pediatric tablets once/d × 3 d 11–20 kg: 1 adult tablet once/d × 3 d 21–30 kg: 2 adult tablets once/d × 3 d 31–40 kg: 3 adult tablets once/d × 3 d >40 kg: 4 adult tablets once/d × 3 d
Mefloquine	15 mg/kg followed 12 h later by 10 mg/kg
Parenteral drug of choice (severe infection): all *Plasmodium* species—CONSULT WITH EXPERTS IN THE MANAGEMENT OF SEVERE MALARIA.	
Quinidine gluconate	10 mg/kg loading dose (max 600 mg) in normal saline over 1–2 h, followed by continuous infusion of 0.02 mg/kg/min until oral quinine sulfate (30 g/kg/d in 3 doses × 7 d) therapy can be started
PLUS either	
Doxycycline	4.4 mg/kg/d in 2 doses × 7 d, preferred oral if tolerated
OR	
Tetracycline	25 mg/kg/d in 4 doses × 7 d
OR	
Clindamycin	20 mg/kg/d in 3 doses × 7 d, preferred oral if tolerated
OR	

Table 1 (*continued*)

Drug	Dosage
Artesunate (followed by one of the following oral agents: atovaquone/proguanil, clindamycin, or mefloquine)	2.4 mg/kg/dose IV × 3 d at 0, 12, 24, 48 and 72 h *(Investigational new drug; contact CDC for information on use.)*
Prevention of relapses: *P vivax* and *P ovale* only	
Primaquine phosphate (must test first for G6PD deficiency)	0.6 mg base/kg × 14 d

Abbreviations: CDC, Centers for Disease Control and Prevention; G6PD, glucose-6-phosphate dehydrogenase; IV, intravenous.

[a] Chloroquine-resistant species include *P falciparum* acquired in most areas and *P vivax* acquired in New Guinea and Indonesia; see CDC for detailed map.

[b] Artemether/lumefantrine tablet: 20-mg artemether and 120-mg lumefantrine. Take with food or whole milk.

Modified in part from American Academy of Pediatrics. *Red Book: 2015 Report of the Committee on Infectious Diseases.* Kimberlin DW, Brady MT, Jackson MA, Long SS, eds. 30th ed. Elk Grove Village, IL: American Academy of Pediatrics; 2015.

Ascariasis

- Treat with
  - Albendazole: 400 mg (single dose)
  - Mebendazole: 100 mg twice daily for 3 days
  - Ivermectin: 200 mcg/kg (single dose)
    - Experience with these 3 drugs is limited in children <2 years.
- Pyrantel pamoate and nitazoxanide are also effective.
- Reexamination of stools after 2 weeks is helpful to assess effectiveness of therapy.
- Patients with suspected intestinal or biliary obstruction
  - Should be managed conservatively with nasogastric suction and IV fluid
- Surgery.
  - If medical therapy is not successful at relieving obstruction or for complications (eg, volvulus peritonitis or perforation).
  - During laparotomy for obstructive cases, small bowel should be "milked" down to the cecum, avoiding incision of bowel wall.
  - Endoscopic retrograde cholangiopancreatography is used to extract worms in hepatobiliary cases.

Toxocariasis

- Albendazole.
  - Approved by the FDA but not for this clinical indication
  - Dose: 400 mg twice a day for 5 days
- Corticosteroids are indicated for cases of severe cardiac and CNS involvement.
- Ocular involvement.
  - Anthelmintic therapy, surgery, steroids, or a combination of these.
  - Diethylcarbamazine is an alternative but is used rarely due to adverse events.

Cestode Infections

Taeniasis

- Praziquantel
  - Drug of choice for the treatment of taeniasis from *T solium* and *Taenia saginata*
  - Highly effective in eradicating the adult stage (intestinal stage) of the tapeworm
  - Not approved for this indication
  - Recommended dose for children: 5–10 mg/kg (single dose)
- Niclosamide and nitazoxanide
  - Alternative agents.
  - Niclosamide is not available commercially in the United States.

Cysticercosis

- In general, albendazole is preferred over praziquantel because of higher cysticidal activity, less interaction with anticonvulsants, and lower cost. Steroids are often given with both.
- Albendazole.
  - Recommended dose: 15 mg/kg/d (maximum dose of 800 mg/d) divided into 2 doses for 8–30 days.
  - Treatment can be repeated as necessary.

- Praziquantel.
  - Recommended dose: 50–100 mg/kg/d in 3 divided doses for 30 days
- An anticonvulsant agent is usually recommended for patients who
  - Present with seizures
  - Have multiple cysts with no history of seizure, because of risk of seizure activity after treatment initiation
- Cysticercal encephalitis.
  - The initial goal is to reduce inflammation and cerebral edema with a corticosteroid or an immunosuppressive agent.
  - Treatment with a cysticidal agent should be deferred because the subsequent inflammatory response may worsen outcome and, in many cases, the cysticerci may resolve with anti-inflammatory therapy alone.
  - A small cyst located in the lateral ventricle can be treated effectively with an anthelmintic agent.
  - Ventriculoperitoneal shunt is recommended before treatment begins in patients with hydrocephalus.
  - If the cyst is in the fourth ventricle, attached to the middle cerebral artery, or compressing the optic chiasm, surgery should be performed before the cysticidal agent is administered.
  - Patients with subarachnoid cysts or a large cyst in the fissures should be treated for ≥30 days.
- Surgery is the mainstay of treatment for ocular and spinal cysticercosis with no clearly defined role of anthelmintic therapy.
- Intraocular subretinal cyst.
  - Treatment with albendazole combined with a corticosteroid may be effective.
  - An intraocular cyst located in the vitreous chamber should be removed surgically.
  - An ophthalmologic examination should be performed in all cases to rule out intraocular cysts before initiating treatment.
- Symptomatic subcutaneous or muscular lesions.
  - Treatment with anti-inflammatory medication.
  - Surgical excision of a solitary subcutaneous or intramuscular cyst may be considered if symptoms persist.

Hymenolepiasis

- Praziquantel is the drug of choice.
- Not FDA approved for this indication.
- Dose: 25 mg/kg (single dose).
- Close family members, especially siblings, may also need treatment.

FOLLOW-UP

- Hookworm infections
  - Repeat stool examination may be performed 2 weeks after treatment.
    - If positive result, consider additional treatment.
- Cysticercosis
  - Neurocysticercosis should be monitored with brain imaging after completion of treatment.
- Hymenolepiasis
  - Stool examination may be repeated 2–4 weeks after treatment.
    - Especially in patients with many worms

COMPLICATIONS

Protozoal Infections

Amebiasis

- Fulminant colitis with bowel necrosis leading to perforation and peritonitis
  - Rare, but associated with mortality rate >40%
- Rare complications
  - Ameboma (a nodular, tumorlike focus of proliferate inflammation in the wall of the colon)
  - Toxic megacolon
  - Local perforation
  - Peritonitis
  - Extraintestinal extension
- Complications of amoebic hepatic abscess
  - Jaundice
  - Extension or rupture into lung, pleural space, peritoneum, or pericardium

Cryptosporidiosis

- The biliary tract is affected in 10%–30% of HIV-infected patients.
  - Can lead to sclerosing or acalculous cholangitis

Toxoplasmosis

- Rare complications of primary toxoplasmosis infection
  - Hepatitis
  - Pneumonitis
  - Myocarditis
  - Pericarditis
  - Encephalitis
- Complications of congenital toxoplasmosis
  - If untreated, a large proportion of infants may develop late-onset sequelae, such as
    - Chorioretinitis: relapses are frequent, and possible vision loss
    - Learning disabilities
    - Intellectual disability months to years later

- Other complications
  - Chorioretinal scars
  - Microphthalmia
  - Cataract
  - Retinal detachment

Babesiosis

- Vascular injury may cause renal insufficiency.

Nematode Infections

Trichinellosis (Severe)

- Fatal myocarditis with subsequent heart failure and cardiac arrhythmias
- Encephalitis
- Meningitis
- Focal neurologic deficits
- Bronchopneumonia
- Nephritis

Ascariasis

- Intestinal complications in endemic areas include ileocecal intussusception, volvulus, intestinal gangrene, and perforation.
- Intestinal obstruction is the primary cause of death in ascariasis.
- Worm migration into the biliary tree can cause biliary colic, cholecystitis, and ascending cholangitis.
- Biliary strictures and hepatic abscesses are less frequent.
- Pancreatitis may result from migration of the adult worm into the pancreatic duct.
- Worm migration to the appendix may lead to appendicitis.
- Worm migration is stimulated by
  - Stress factors, such as fever, intercurrent illness, diarrhea, spicy foods, and anesthesia
  - Some anthelmintic agents

Toxocariasis

- Complications of ocular larva migrans
  - Chronic endophthalmitis
  - Retinal detachment
  - Keratitis
  - Uveitis
  - Iritis
  - Vitreous abscess
  - Optic neuritis
  - Retinal tracks with larvae

Cestode Infections

Cysticercosis

- After treatment initiation, patients may develop a treatment reaction, usually with an inflammatory reaction in the surrounding tissue.
  - Severe headache and vomiting.
  - Reaction can be minimized by administration of dexamethasone 2–3 days before treatment initiation and during treatment with a cysticidal agent.

PROGNOSIS

- Amoebic meningoencephalitis
  - PAM
    - Even with combined therapy, survival has been the exception.
- Cryptosporidiosis
  - In immunocompromised patients, particularly those infected with HIV
    - Cryptosporidiosis frequently takes a severe and protracted course.
    - Can lead to significant malnutrition and wasting, dehydration, and death.

PREVENTION

Protozoal Infections

Amoebic Meningoencephalitis

- Avoidance of swimming in warm, stagnant, and possibly feces-contaminated waters
- Proper chlorination of swimming pools and avoiding diving and direct introduction of water to the nostrils
- Proper contact lens care procedures

Cryptosporidiosis

- Effective hand washing and appropriate disposal of infected material.
- Appropriate water filter to prevent or control an outbreak.
- Contact precautions for diapered and incontinent children.
- Infected people should not use public recreational water when they have diarrhea and for ≥2 weeks after symptoms resolve.
- Boiling drinking water for 1 minute kills *Cryptosporidium*.
  - Alternatively, filtration devices with particle-size ratings of 1–5 mcm are effective for removing *Cryptosporidium* species.

Toxoplasmosis

- General measures
  - Hygienic practices during cat contact.
  - Avoidance of raw meat.
    - Deep freezing to -12.0°C (10.4°F) for 24 hours and cooking meat, particularly ham and lamb, to internal temperature of 65.5°C–76.6°C (149.9°F–169.9°F) or until no longer pink to kill cysts.
    - Thorough washing of all fruits and vegetables.
    - Avoid ingesting untreated water, especially in developing countries.
  - Pregnant women and immunocompromised individuals should avoid contact with cats, cat litter, or soil contaminated by cat feces.
    - Stress wearing gloves and hand washing in such settings.
    - Cats may be prevented from acquiring infection by restricting outdoor activities and feeding commercially prepared cat food.
    - Because oocysts are not infective until 36–48 hours or longer after passage, daily cleaning of cat litter boxes is a simple and effective control measure.
- Prophylactic therapy
  - Children with HIV or AIDS with severe immunosuppression and positive *Toxoplasma* IgG antibodies
    - The drug of choice is trimethoprim-sulfamethoxazole.
    - Alternative therapies: dapsone plus pyrimethamine (with supplemental folinic acid) or atovaquone.
  - To prevent recurrence of toxoplasmosis in immunosuppressed patients with prior *Toxoplasma* encephalitis
    - Pyrimethamine plus sulfadiazine plus folinic acid
    - Alternatively, clindamycin plus pyrimethamine plus folinic acid or atovaquone for patients who cannot tolerate sulfa drugs

Malaria

- To prevent recurrence after treatment of an episode of *P vivax* or *P ovale* malaria.
  - Drugs that target the liver should be added to minimize the likelihood of recurrence.
    - Patients should be checked for glucose-6-phosphate dehydrogenase (G6PD) deficiency before being given primaquine.
- Reducing population of *Anopheles* mosquitoes (vector control).
- Avoiding bites by parasite-carrying mosquitoes.
- Providing prophylactic antimalarial drugs.
- Detailed guidelines about chemoprophylaxis of malaria for travelers to endemic areas are available at www.cdc.gov/travel.

Chemoprophylaxis by Geographic Area

- Begin 1 week before arrival in area with endemic infection (except doxycycline and atovaquone-proguanil, which should be started 1–2 days before arrival) to allow time to develop blood concentrations of the drug and evaluate for adverse reactions.
- Medications should be continued after departure from endemic area (chloroquine and mefloquine for 4 weeks after return; atovaquone-proguanil for 7 days after return; and doxycycline for 28 days after return).
- Areas with chloroquine-sensitive *Plasmodium* species.
  - Chloroquine phosphate: 5 mg base/kg once a week; up to adult dose of 300 mg base
- Areas with chloroquine-resistant *Plasmodium* species.
  - Atovaquone/proguanil
    - 5–8 kg: ½ pediatric tablet/d
    - >8–10 kg: ¾ pediatric tablet/d
    - 11–20 kg: 1 pediatric tablet/d
    - 21–30 kg: 2 pediatric tablets/d
    - 31–40 kg: 3 pediatric tablets/d
    - >40 kg: 1 adult tablet/d
  - *Or* mefloquine
    - 11–20 kg: 0.25 tablet once a week
    - 21–30 kg: 0.50 tablet once a week
    - 31–45 kg: 0.75 tablet once a week
    - >45 kg: 1 tablet once a week
  - *Or* doxycycline: 2 mg/kg/d, up to 100 mg/d (children >8 years only)
  - Alternatives: primaquine: 0.6 mg base/kg daily (Must test for G6PD deficiency and confirm that the patient is not deficient before use.)

Babesiosis

- Avoid tick-infested areas.
  - Particularly from May to September
- Wear clothing that covers arms, legs, and other exposed areas.
  - Tuck pants into socks or boots.

- Tick and insect repellents that contain *N,N*-diethyltoluamide (DEET) may be considered. Others include picaridin, IR-3535, and oil of lemon eucalyptus.
  - Repeat applications as needed.
- Tick-toxic agents, such as permethrin, may be sprayed on clothes and shoes but not the skin.
- Inspect bodies of self and children, as well as all clothing, for ticks after possible exposure.
  - Exposed hairy areas, including scalp and behind the ears, should be inspected thoroughly.
- If a tick is found
  - Grasp with tweezers close to the skin and gently pull out straight.
- Pets should be inspected for ticks daily; remove any ticks identified.

Nematode Infections

Trichinellosis

- Thorough cooking of pork and game meat
  - Heat at a temperature of 77.0°C (170.6°F).
- Freezing is effective in killing larvae in meat.
  - Freezing at -15°C (5°F) for 3 weeks (available in home freezers)
  - Freezing pork at -23.0°C (-9.4°F) for 10 days

Hookworm Infections

- Proper disposal of human feces

Ascariasis

- Sanitary disposal of human feces is essential to prevent soil contamination.
  - Particularly near children's play areas
- Mass deworming programs with a single dose of mebendazole or albendazole have been used in some communities endemic for ascariasis.

Toxocariasis

- Correct underlying causes of pica in children.
- Cat and dog feces should be properly disposed of.
- Sandboxes not in use should be covered.
- Regular anthelmintic therapy for puppies and kittens may prevent secretion of eggs in feces and subsequent potential transmission.

Pertussis (Whooping Cough)

DEFINITION

- A highly contagious, bacterial respiratory infection
  - Caused by *Bordetella pertussis,* an aerobic gram-negative coccobacillus
  - Characterized by paroxysms of intense coughing and a protracted clinical course lasting several weeks

SIGNS AND SYMPTOMS

Infants and Children

- 3 stages of illness, each lasting at least 2 weeks.
- Classic stages are evident most commonly in unimmunized infected young children.
  - In partially or totally immunized children, stages are shortened and may be atypical.
  - Neonates do not have an apparent catarrhal phase.
- Incubation period of 7–10 days.
- Catarrhal phase.
  - Nonspecific upper respiratory tract symptoms with
    - — Rhinorrhea
    - — Lacrimation
    - — Mild cough
    - — Conjunctival injection
- Paroxysmal stage.
  - Intermittent dry hacking cough.
  - Repetitive series of forceful coughs within a single expiration.
  - Sudden massive inspiratory respiratory effort often occurs at the end of a cough paroxysm, resulting in a high-pitched whoop.
  - Between attacks, patient appears comfortable, without apparent distress.
  - Very young infants often lack the characteristic whoop and exhibit episodes of
    - — Gagging
    - — Gasping
    - — Apnea
    - — Bradycardia
    - — Cyanosis
- Convalescent stage.
  - Diminishing severity and frequency of paroxysms
  - Continued intermittent coughing for weeks to months, often exacerbated by subsequent intercurrent respiratory illness
- Physical examination is usually typical, except for evidence of the forcefulness of their cough and posttussive emesis.
  - Conjunctival hemorrhage
  - Upper body petechial lesions
- Fever.
  - Characteristically absent at all stages
  - If present, suggests secondary bacterial infection

Adolescents and Adults

- Usually does not have distinct phases.
- Persistent (>21 days) cough, indistinguishable from other respiratory infections, can be the only symptom.
- Paroxysmal nature of the cough is present in ~70%–99% of infected individuals.
- Other features include
  - Inspiratory whoop
  - Posttussive emesis
  - Choking
  - Sleep disturbed by cough
- Positive predictors of confirmed pertussis include
  - History of prolonged duration of violent cough (median, 43 days)
  - Longer duration of cough illness (median, 56 days)
  - Posttussive emesis
- Adults with pertussis do not have fever.

DIFFERENTIAL DIAGNOSIS

In Infants

- Respiratory viral illnesses
- Infection with *Chlamydia trachomatis* and with other *Bordetella* species
- Bacterial pneumonia
- Foreign body aspiration
- Reactive airways disease
- Adenovirus
  - Can produce clinical syndrome of
    - — Prolonged paroxysmal cough
    - — Posttussive emesis
    - — Inspiratory whoop
  - Presence of associated features commonly found with adenovirus can help distinguish clinically
    - — Pharyngitis
    - — Conjunctivitis
- Respiratory syncytial virus (RSV)
  - A common cause of upper and lower respiratory tract infection in neonates and infants.
  - Dual infection with RSV and *B pertussis* can occur.
    - — Apnea is a common complication of both infections.
  - Predominantly lower respiratory tract signs (wheezing), fever, and ongoing symptoms between cough episodes more suggestive of RSV.

- *C trachomatis*
  - A common cause of afebrile pneumonia in young infants
  - Infants with chlamydial infection usually have
    - Staccato rather than paroxysmal cough
    - Lower respiratory tract signs, such as tachypnea and rales
    - Frequent history of neonatal conjunctivitis
- *Bordetella parapertussis* and, rarely, *Bordetella bronchiseptica*
  - Characteristically cause a less protracted illness
- Bacterial pneumonia caused by *Staphylococcus aureus* and *Streptococcus pneumoniae*
  - Not difficult to distinguish based on the clinical manifestations.
    - High temperature
    - Ill appearance
    - Respiratory distress
  - These agents can secondarily complicate pertussis infection.

In the Older Child, Adolescent, and Adult

- Adenoviral infection.
- *Mycoplasma pneumoniae.*
  - Common cause of prolonged cough and may be difficult to distinguish
  - Suggested by presence of systemic symptoms, such as
    - Headache
    - Sore throat
    - Rales on auscultation of the chest
    - Chest radiograph that characteristically appears worse than the appearance of the patient would indicate
- *Chlamydophila pneumoniae.*
- Reactive airways disease.
- Upper respiratory tract infection.
- Concurrent outbreaks have been reported.

DIAGNOSTIC APPROACH

- Definitive diagnosis of pertussis is problematic.
- A complete history is by far the most important aspect of the evaluation of the infant or child with possible pertussis.
- Clinical diagnosis can be supplemented by
  - Physical examination
  - Laboratory studies
  - Radiographic studies
- Physical examination is usually typical.
- Diagnosis may be missed if attention is not paid to the historical description of coughing paroxysms.
- Cough paroxysms in a young infant should be witnessed by a medical professional before a disposition is planned.

LABORATORY FINDINGS

- Culture
  - Isolation of the organism by culture is the diagnostic standard.
    - Highly dependent on appropriate specimen collection, transport, and isolation technique
  - Culture is obtained from the posterior nasopharynx using a calcium alginate or Dacron-tipped (not cotton-tipped) swab.
  - Specimen should be immediately inoculated onto Regan-Lowe medium and incubated for 7 days.
  - Semisolid transport media is available if the specimen cannot be inoculated immediately onto solid media.
  - Even in ideal conditions, sensitivity of culture is suboptimal.
    - Most likely to be positive early in the illness (catarrhal and early paroxysmal phase) in unimmunized children
    - Greatly diminished when obtained late in the illness, in immunized individuals, and in those who have received macrolides or sulfonamides
- Polymerase chain reaction (PCR) testing
  - Nasopharyngeal specimens.
  - Appears to be more sensitive than culture, including in individuals who are mildly symptomatic and in those who have been treated with macrolides.
  - Sensitivity highly dependent on the age of the patient; likely a reflection of past immunization and immune responses.
    - 60%–70% sensitive in infants and young children
    - <10% sensitive in older children and adults
  - PCR also can detect *B parapertussis*.
- Direct fluorescent antibody testing for pertussis antigens
  - Nasopharyngeal specimens
  - Plagued by poor sensitivity when compared with culture
  - Requires experienced laboratories for accuracy
  - Rarely used today

- Serologic testing for detection of antibodies to components of *B pertussis* in acute and convalescent samples
  - The most sensitive mode of diagnosis.
  - Used extensively in epidemiologic studies and vaccine trials.
  - Not readily available.
  - Results are difficult to interpret in immunized individuals.
  - Not helpful for the diagnosis of pertussis.

IMAGING

- Chest radiography in infants and children
  - Commonly normal
  - May reveal
    - — Perihilar infiltrates
    - — Pneumothorax
    - — Pneumomediastinum

TREATMENT APPROACH

- Supportive care is the mainstay of management.
- Hospitalization is indicated for most infants <6 months.
  - To assess for life-threatening events associated with paroxysms, such as
    - — Apnea
    - — Bradycardia
    - — Hypoxia
- Hospitalization provides
  - Continuous cardiorespiratory monitoring
  - Vigilant suctioning of the nasopharynx
  - Oxygen therapy, if needed
  - Careful attention to feeding and hydration
  - Monitoring and treatment of acute complications
- A macrolide antibiotic is indicated for proven or suspected pertussis to
  - Eliminate the organism from the nasopharynx.
  - Limit spread to others.
- If administered early, this therapy can reduce duration and severity of symptoms.
- These agents have little influence on clinical course of pertussis unless use is started early in the catarrhal phase.

SPECIFIC TREATMENTS

Macrolide Agents

- Erythromycin traditionally has been the antibiotic of choice.
- Newer macrolide agents clarithromycin and azithromycin are
  - As effective
  - Better tolerated
  - Associated with fewer and milder adverse effects
- Based on these data, the Centers for Disease Control and Prevention developed guidelines recommending that erythromycin, clarithromycin, and azithromycin be used for the treatment of pertussis in persons ≥1 month.
- Although studies evaluating the safety and efficacy of the newer macrolides for infants <6 months are limited, their use is encouraged based on
  - In vitro effectiveness
  - Demonstrated safety in older infants and children
  - More convenient dosing schedule
- Erythromycin therapy is associated with infantile hypertrophic pyloric stenosis.
  - Thus azithromycin is the preferred macrolide in neonates <1 month.
  - Limited data to date have not documented an association between azithromycin and infantile hypertrophic pyloric stenosis.

Antimicrobial Treatment and Postexposure Prophylaxis by Age Group

- Treatment of parapertussis is the same as for pertussis (**Table 1**).

Care of Household and Other Close Contacts

- A macrolide should be given promptly to all household and close contacts (eg, those in child care).
- Chemoprophylaxis.
  - Significantly reduces but does not eliminate risk of pertussis
  - Should be given to close contacts regardless of age and immunization status
  - Should be given to health care workers with definite or likely exposure
- Antimicrobial agents that should be used for postexposure prophylaxis are the same as for treatment.
- Trimethoprim-sulfamethoxazole (TMP-SMX).
  - An alternative treatment or prophylactic option for patients who cannot tolerate macrolides.
  - Contraindicated in infants <2 months.
  - The dosing regimen for TMP-SMX is
    - — ≥2 months: TMP, 8 mg/kg/d; SMX, 40 mg/kg/d in 2 doses for 14 days
    - — Adolescents and adults: TMP, 320 mg/d; SMX, 1,600 mg/d in 2 divided doses for 14 days
  - The treatment for *B parapertussis* is the same.

Table 1. Antimicrobial Treatment and Postexposure Prophylaxis for Pertussis by Age Group

Age Group	Recommended Agent
<1 mo	Azithromycin 10 mg/kg/d as single daily dose for 5 days
1–5 mo	Azithromycin 10 mg/kg/d as single daily dose for 5 days, OR erythromycin 40–50 mg/kg/d in 4 divided doses for 14 days, OR clarithromycin 15 mg/kg/d in 2 divided doses for 7 days
Infants ≥6 mo and children	Azithromycin 10 mg/kg/d as single dose on day 1, then 5 mg/kg/d (maximum 500 mg) on days 2–5, OR erythromycin 40–50 mg/kg/d (maximum 2 g/d) in 4 divided doses for 14 days, OR clarithromycin 15 mg/kg/d in 2 divided doses (maximum 1 g/d) for 7 days
Adolescents and adults	Azithromycin 500 mg as single daily dose on day 1, then 250 mg/d on days 2–5, OR erythromycin 2 g/d in 4 divided doses for 14 days, OR clarithromycin 1 g/d in 2 divided doses for 7 days

Adapted from Tiwari T, Murphy TV, Moran J; Centers for Disease Control and Prevention National Immunization Program. Recommended antimicrobial agents for the treatment and postexposure prophylaxis of pertussis: 2005 CDC guidelines. *MMWR Recomm Rep.* 2005;54(RR-14):1–16.

WHEN TO ADMIT

- Strongly consider in any infant <6 months suspected of having pertussis.
- When complications such as apnea, bacterial pneumonia, bradycardia, or pulmonary hypertension exist.
- When the infant has an oxygen requirement or when the infection is interfering with feeding.

COMPLICATIONS

- Secondary bacterial pneumonia is the most common complication.
  - Occurs in ~5% of all reported cases
  - Causes most pertussis-related deaths
- Infants <6 months have highest rate of hospitalization (69%), secondary bacterial pneumonia (13%), and seizures (2%).
- Important complications include
  - Apnea
  - Bradycardia
  - Dehydration
  - Pulmonary hypertension
  - Pneumothorax
  - Central nervous system changes
  - Retinal hemorrhages
- Complications are much more common in infants.
- In adults, morbidity includes
  - Pneumonia
  - Otitis media
  - Sinusitis
  - Rib fracture
  - Pneumothorax
  - Pneumomediastinum
  - Weight loss
  - Urinary incontinence

PROGNOSIS

- Young infants have the highest incidence of morbidity and mortality.
  - 91% of pertussis-related deaths occur in infants <6 months.

PREVENTION

- The American Academy of Pediatrics (AAP) recommends universal immunization with pertussis vaccines for children <7 years.
  - Vaccination of all children starting in infancy has resulted in >97% decrease in incidence of pertussis in the United States.
- Currently available acellular vaccines have been shown to be 75%–90% effective and well tolerated.
  - Purified subunit vaccines
  - Combination vaccines with diphtheria and tetanus toxoids (Td)
- The AAP recommends that a total of 5 doses of pertussis vaccine be administered to every child before school entry, unless contraindicated.
  - First dose at 2 months of age
  - 2 subsequent doses at intervals of 2 months
  - Fourth dose at 15–18 months
  - Fifth dose at 4–6 years

- Because of the role that adolescents and adults play in transmission, studies have evaluated efficacy and safety of acellular pertussis vaccines in these age groups.
  - Adverse reactions to these vaccines among adolescents and adults have been mild.
  - Although these vaccines appear well tolerated in trials to date, concern exists about the possibility of more severe limb swelling in individuals vaccinated with booster doses of acellular vaccines after primary immunization with the same acellular vaccines.
    - However, limb swelling does not appear to be a problem in those who received whole-cell vaccine as their primary immunization.
  - Thus, adolescents and adults who previously received acellular vaccines will need to be observed closely when given booster doses to determine the frequency and severity of such reactions.
- The AAP recommends that adolescents aged 11–18 years receive acellular pertussis vaccine combined with tetanus and reduced diphtheria toxoid (Tdap).[1]
  - Single dose of Tdap instead of Td vaccine for booster immunization for adolescents 11–18 years of age.
  - The preferred age for Tdap immunization is 11–12 years.
  - Adolescents 11–18 years of age who have received Td but not Tdap are encouraged to receive a single dose of Tdap.
  - An interval of 2 years between Td and Tdap immunization is suggested; however, Tdap can be given at shorter intervals in settings of increased risk of pertussis, such as for a close contact with a case, outbreak setting, and close contact with an infant.
  - Children between 7 and 10 years of age who have not completed their primary immunization schedule or have an unknown vaccine history should receive a single dose of Tdap.

REFERENCE

1. Adapted from American Academy of Pediatrics. Pertussis (whooping cough). In: Kimberlin DW, Brady MT, Jackson MA, Long SS, eds. *Red Book: 2015 Report of the Committee on Infectious Diseases.* 30th ed. Elk Grove Village, IL: American Academy of Pediatrics; 2015:608–621

DEFINITION

- Petechiae
  - Small (1–3 mm), red, non-blanching macular lesions caused by intradermal capillary bleeding
- Purpura
  - Larger, typically raised lesions resulting from bleeding within the skin

HISTORY

- Evaluation begins with a complete history.
  - Can readily eliminate most disorders from the differential diagnosis
- Special attention to
  - Recent trauma
  - Bleeding history
  - Medication use
  - Symptoms consistent with
    - Infection
    - Malignancy
    - Autoimmune disorders
    - Vasculitic disorders
    - Connective tissue disorders
    - Rheumatologic disorders

PHYSICAL EXAMINATION

- Petechiae
  - Small (1–3 mm), red, non-blanching macular lesions
- Purpura
  - Larger.
  - Typically raised lesions.
  - Can vary somewhat in color.
    - Based on the age of the lesion as the blood within the skin is metabolized
  - Do not blanch.
  - May occur anywhere on the body.
- Physical examination should determine
  - If skin findings are isolated
  - If evidence of a more generalized process is present
- Particular physical findings to evaluate include
  - Hepatosplenomegaly
  - Lymphadenopathy
  - Arthritis
  - Arthralgias
  - Findings consistent with an acute viral syndrome

DIFFERENTIAL DIAGNOSIS

General

- Neither petechiae nor purpura are pathognomonic of a specific disorder.
- Petechiae and purpura must be evaluated according to
  - Overall context of the patient—age and history
  - Severity and extent of lesions
- Physician must entertain a broad differential diagnosis.
  - Hemostasis
  - Infection
  - Autoimmune disorders
  - Trauma
  - Malignancy
  - Other rare causes, such as vasculitis and connective tissue disorders
- Underlying pathophysiological mechanism may be defined by
  - Age at presentation
  - Overall appearance
  - Extent of the lesions
- Scant petechiae on the face of an otherwise well-seeming newborn after a vaginal delivery are likely caused by the trauma of passing through the birth canal.
  - Newborn with diffuse petechiae warrants further evaluation.
- If the child seems ill
  - Sepsis must be strongly considered.
- If the child seems well
  - Platelet disorder should be considered.
- With petechiae or purpura, the possibility of a hemostatic defect is always a concern.
  - For isolated petechiae, the physician must consider a primary platelet disorder.
    - Low platelet number
    - Platelet dysfunction
  - Purpura may result from a platelet disorder or other coagulation defect.
    - Can be classified as primary or as a secondary phenomenon from an underlying disease
  - Platelet disorders can be classified as disorders of
    - Platelet production
    - Platelet survival (destruction)
    - Platelet function
- Easy bruising and bleeding may be manifestations of disorders unrelated to clotting and platelets.
  - In connective tissue disorders, bruising is related to fragile capillaries and perivascular connective tissues rather than a hemostatic defect.

- Normal platelet count is 150,000–450,000/mm^3.
- Low platelet counts.
  - >80,000: Child will be hemostatically normal as long as platelet function is not altered.
  - 50,000–80,000: Increased bleeding with trauma is likely, but spontaneous bleeding would be unusual.
  - 20,000–50,000: A mild bleeding diathesis is expected.
  - <20,000: Spontaneous mucosal bleeding can occur.
  - <10,000: Spontaneous severe bleeding is a danger.

Infectious Causes of Petechiae and Purpura

- In an ill-appearing child with petechiae or purpura, appropriate antibiotics should be administered based on likely pathogens.
  - Bacterial meningitis must be considered for the febrile child with petechiae or purpura.
  - In children with bacteremia and sepsis, platelet consumption is common before frank disseminated intravascular coagulation (DIC) has developed.
  - Purpura fulminans has been associated with *Streptococcus* and *Meningococcus* species, as well as with viral infections.
    - Microscopic thromboses in arterioles result in purpura, infarction, and bleeding within the skin and subcutaneous tissue.
    - These lesions may coalesce and become necrotic, and patients typically develop full DIC.
- Mechanism by which a variety of viruses cause thrombocytopenia is not clear.
  - May involve
    - Decreased platelet production
    - Immune-mediated destruction
  - Live-virus vaccinations can cause moderate thrombocytopenia.
    - Varicella
    - Measles
  - Cytomegalovirus has been implicated in thrombocytopenia.
    - Treatment of cytomegalovirus has not affected the outcome of patients monitored for chronic thrombocytopenia.
  - Parvovirus has been associated with
    - Isolated thrombocytopenia
    - Pancytopenia
  - Dengue and other viral hemorrhagic fevers are known to cause thrombocytopenia.
    - Patients may develop petechiae and purpura as a result.
  - HIV has been associated with thrombocytopenia from bone marrow suppression and immune-mediated destruction.
- Rickettsial diseases, such as Rocky Mountain spotted fever, may produce a petechial rash.
  - Alterations of the endothelial lining of blood vessels cause
    - Thrombi formation
    - Platelet destruction
  - Thrombocytopenia and DIC may develop.
- Malaria can cause mild or profound thrombocytopenia—mechanisms are not well defined.

Disorders of Platelet Production: Malignancy and Bone Marrow Failure Syndrome

- Most patients with petechiae or purpura have a benign process.
  - The greatest concern for physician and parents is malignancy.
- History must rule out the classic signs and symptoms of malignancy.
  - Fevers
  - Night sweats
  - Weight loss
  - Lymphadenopathy or other masses
  - Pallor
  - Malaise
  - Bone pain
  - Anorexia
- Many of these symptoms overlap with those seen in infectious and autoimmune processes.
- Petechiae or purpura in the setting of hepatosplenomegaly or impressive lymphadenopathy would put leukemia high on the differential diagnosis.
- Other marrow infiltrating malignancies must be considered.
- Petechiae and purpura may be the presenting signs in patients with bone marrow failure secondary to nonmalignant processes.
  - Abnormal hematopoiesis usually causes *pancytopenia,* defined as alteration of >1 cell line, or even all cell lines.
  - Bone marrow failure may occur secondary to
    - Infectious processes
      - Viral
      - Bacterial with sepsis
    - Medication use, notably a variety of antibiotics and anticonvulsants
    - Profound nutritional deficits

- Rare bone marrow failure syndromes
  - Fanconi syndrome
  - Myelodysplastic disease
  - Wiskott-Aldrich syndrome

Disorders of Platelet Function: Primary Platelet Disorders

- Petechiae and purpura may result from a primary platelet disorder.
- Qualitative disorders result from platelet dysfunction.
  - Absolute platelet number is normal.
  - Platelets lose normal hemostatic function.
  - In most instances, platelet dysfunction is acquired from medication use.
  - Classic example is aspirin, which causes irreversible inhibition of cyclooxygenase within platelets.
  - Other causes of acquired platelet dysfunction include
    - Uremia
    - Liver disease
  - Mechanisms of poor platelet function in these settings are not clear.
- von Willebrand disease.
  - Not a primary platelet disorder.
  - Patients commonly present with painless, mucocutaneous bleeding.
  - Should be considered in patients who have
    - Petechiae and purpura
    - Reference platelet count
    - No other obvious systemic disease
  - Most common bleeding disorder.
    - Affects ~1% of the population.
  - Establish the diagnosis with
    - Coagulation screening
    - Factor VIII and von Willebrand factor assays
- Variety of rare platelet function disorders can be considered in patients with
  - Reference platelet number
  - Bleeding
  - Petechiae or purpura
  - Can be diagnosed with
    - Specialized platelet aggregation studies
    - Morphologic study of platelets
  - Hematology consultation should be made to define disorders such as
    - Glanzmann thrombasthenia
    - Bernard-Soulier syndrome (inherited platelet disorder with variable thrombocytopenia)
    - Hermansky-Pudlak syndrome
    - Chédiak-Higashi syndrome

Disorders of Platelet Survival (Destruction)

- Isolated thrombocytopenia in an otherwise well child may lead to petechiae or purpura as the chief complaint.
- Idiopathic (or immune) thrombocytopenic purpura is a diagnosis of exclusion.
  - Produces profound isolated thrombocytopenia and petechiae or purpura.
  - Few other findings on physical examination.
  - Laboratory workup should be normal except for thrombocytopenia.
    - No other blood cell line is affected.
  - Microscopic review of the blood reveals platelets that are too few in number but large in size.
    - Indicates that they are young.
    - Platelet life span is reduced to minutes or hours rather than the normal several days.
  - Incidence is highest in children 2–8 years of age.
  - Formerly, physicians performed bone marrow aspirates to rule out malignancy or other bone marrow failure syndromes.
    - Most now think that the diagnosis can be made clinically.
    - Bone marrow studies rarely are indicated.
- Typically, one-third of the total body platelet mass is sequestered within the spleen at any time.
  - Whatever the cause of increased spleen size, mild thrombocytopenia may result.
  - Common causes of hypersplenism include
    - Liver disease
    - Variety of infections, such as Epstein-Barr virus, malaria
    - Metabolic diseases, such as Gaucher disease
  - Hypersplenism alone does not typically cause platelet counts <50,000.
    - Alternative explanations should be considered for patients with moderate to severe thrombocytopenia.
- Henoch-Schönlein purpura.
  - Autoimmune vasculitic syndrome
  - Produces purpura in most patients
    - Classic distribution is on the buttocks and legs.
    - May be more disseminated.
  - Other findings in Henoch-Schönlein purpura
    - Arthritis
    - Arthralgias
    - Abdominal pain
    - Renal impairment

- Hemolytic-uremic syndrome.
  - Produces a constellation of findings
    - Thrombocytopenia
    - Hemolytic anemia
    - Renal failure
  - Associated with a variety of infections, most notably *Escherichia coli* O157:H7
- Thrombotic thrombocytopenic purpura.
  - Distinct syndrome rarely seen in children
  - Shares some clinical features with hemolytic-uremic syndrome
  - Findings include
    - Purpura
    - Thrombocytopenia
    - DIC
    - Hemolytic anemia
    - Thrombotic stroke
    - Elevated lactate dehydrogenase
- Giant vascular malformations may cause intravascular destruction of platelets.
  - Kasabach-Merritt syndrome is a classic example of a giant hemangioma causing severe thrombocytopenia secondary to platelet destruction.
  - Lesions usually are readily apparent.
    - Multiple smaller vascular malformations that are more difficult to define may cause platelet destruction.
- Thrombocytopenia or altered hemostasis may be associated with rare vascular disorders and connective tissue syndromes in the absence of coagulopathy, such as
  - Hereditary telangiectasias
  - Ehlers-Danlos syndrome
  - Marfan syndrome
  - Osteogenesis imperfecta

P

LABORATORY EVALUATION

- History and physical examination dictate the appropriate laboratory evaluations.
- At minimum
  - Complete blood cell count with platelets and differential count
  - Prothrombin time and partial thromboplastin time
- When bacterial infection is a consideration, appropriate cultures.
- Isolated profound thrombocytopenia is not likely to result from a malignancy.
- When >1 cell line on a blood cell count is abnormal, bone marrow process must be considered.
- If the history or physical examination is consistent with a malignancy, the following evaluations should be obtained immediately:
  - Complete blood cell count
  - Screening coagulation studies
  - Comprehensive metabolic panel
  - Liver function tests
  - Lactate dehydrogenase
  - Uric acid
  - Manual differential count of the peripheral blood
- Laboratory findings consistent with malignancy include
  - Elevated lactate dehydrogenase
  - Elevated uric acid
  - Abnormal serum electrolytes
    - May result from tumor lysis even before therapy is started
- Absence of leukemic blasts on a peripheral blood smear does *not* rule out leukemia.
- Diagnosis of leukemia can be made if peripheral blasts are present.
  - Having few or no peripheral blasts seen on routine microscopy is not uncommon for patients with leukemia.

IMAGING

- Chest radiograph should be obtained immediately when marrow infiltrating malignancy is a consideration.
  - Patient may have occult but massive mediastinal lymphadenopathy.

DIAGNOSTIC PROCEDURES

- Bone marrow aspiration and biopsy
  - Indicated to rule out malignancy and define abnormal hematopoiesis

WHEN TO REFER

- Platelet count <100,000/mm^3
- Diffuse petechiae or purpura
- Focal petechiae or purpura not clearly associated with trauma
- Evidence of >1 cell line abnormality on complete blood cell count

WHEN TO ADMIT

- Toxic-appearing patient
- Moderate to severe bleeding
- Concern for poor adherence

DEFINITION

- *Pharyngitis* implies inflammation of the throat with or without presence of exudate.
- The terms *tonsillitis, tonsillopharyngitis,* and *pharyngotonsillitis* are used when the tonsils are affected.

SIGNS AND SYMPTOMS

- A clinical complaint of sore throat indicates some degree of pharyngitis.

Viral Causes

- Nasopharyngitis and tonsillitis caused by adenoviruses can be exudative.
- Pharyngoconjunctival fever.
  - Cough
  - Myalgias
  - Conjunctivitis
- Herpangina.
  - Typified by pharyngitis associated with small, shallow, erythematous, ulcerated areas on soft palate and peritonsillar region
  - Coxsackieviruses A and B and echovirus
  - Often accompanied by respiratory symptoms
- Epstein-Barr virus (EBV).
  - White, shaggy membrane on tonsils and palatal petechiae
  - In older children, EBV infection is frequently accompanied by
    - Fever
    - Adenopathy
    - Malaise
    - Swelling of the eyelids
    - Generalized rash
    - Hepatosplenomegaly
- Herpes simplex
  - Most oral colonization and covert infection with herpes simplex virus type 1 is asymptomatic.
  - Virus can cause painful gingivostomatitis and pharyngitis in ~1% of infected children.

Bacterial Causes

- Group A β-hemolytic streptococcus (GABHS)
  - Sudden onset of
    - Fever.
    - Sore throat.
    - Dysphagia.
    - Other associations include headache and abdominal pain.
  - Examination of throat reveals an erythematous pharynx and tonsillar area.
    - Often with exudate present
  - Small petechiae (enanthema) are sometimes seen on uvula and soft palate.
  - Cervical lymph nodes are usually enlarged and tender.
  - Symptoms can last for 4–5 days.
    - Gradually subsiding when no antibiotic therapy is instituted
  - Key findings.
    - Red throat or tonsils or exudative tonsils
    - Swollen and usually tender anterior cervical nodes
    - Fever
    - Scarlet fever rash
- *Neisseria gonorrhoeae*
  - Exudative tonsillitis is rarely seen with pharyngitis caused by *N gonorrhoeae*.
- *Corynebacterium diphtheriae*
  - Characteristic gray pseudomembranous exudate over the posterior pharynx and tonsils
- *Arcanobacterium haemolyticum*
  - Physical findings are identical to those seen with GABHS infection.
  - Includes a scarlatiniform rash present in ~20% of cases.
  - Sore throat may persist until patients are treated with antibiotics.

DIFFERENTIAL DIAGNOSIS

- Sore throats are common in children.
  - May be sole finding in an illness
- Streptococcal infections should be considered in children >3 years who have pharyngitis.
  - Even if no exudate is present.
  - Pharyngitis associated with nasal, chest, or cold symptoms is much more likely to be a viral illness.
- In atypical pharyngitis, in duration or severity, suspect
  - Infectious mononucleosis
  - One of the rarer bacterial causes
    - Including those that are sexually transmitted
- Peritonsillar abscess or cellulitis also may cause a sore throat.
  - Thorough examination will reveal
    - Swelling extending into the soft palate
    - Deviation of the uvula
    - Change in tonal quality of the voice
- Postnasal drip from viral respiratory tract infection or allergies has been thought to irritate the posterior pharynx.
  - This finding is not well documented.

- Allergies may lead to chronic inflammation of the mucous membranes, which might include the pharynx.
  - Pharyngitis would be infrequent as the sole manifestation.
- Epiglottitis.
  - Diagnosis that must not be missed
  - Can be life threatening
  - The child with epiglottitis
    - Has severe throat pain
    - Rapidly becomes ill
    - Appears to have a toxic condition
    - Experiences respiratory distress accompanied most often by stridor, although a croupy cough may be present
- Kawasaki disease.
  - Unknown cause.
  - Occurs mostly in preschool children who have
    - Pharyngitis associated with erythema and fissuring of the lips
    - Palmar and pedal edema
    - Erythema
  - An association with staphylococcal toxin has been postulated, as have other viral and bacterial etiologies.
- Oral thrush.
  - In otherwise healthy children, severe mouth pain can occur.
  - May be interpreted as a sore throat.
- Pharyngitis may be associated with other inflammatory conditions of the mucous membranes.
  - Herpes gingivostomatitis
  - Herpangina
  - Stevens-Johnson syndrome

DIAGNOSTIC APPROACH

- The major step is to establish whether GABHS is the responsible pathogen.
  - Almost all children >3 years need to be examined to rule out GABHS as the cause.
  - Multiple studies have shown that streptococcal pharyngitis cannot be distinguished purely on clinical grounds.

LABORATORY FINDINGS

Rapid Streptococcal Test and Cultures

- Traditional method for determining whether the cause of pharyngitis or tonsillitis is viral or GABHS was to obtain a throat swab and perform a culture.
  - With availability of rapid streptococcal tests, the process was made simpler.
    - Allows a result to be obtained in minutes rather than waiting 1–2 days.
    - Strict federal guidelines for office laboratories require certification for use of these rapid tests.
    - Most clinicians now perform a rapid streptococcal diagnostic test on all patients whose pharyngitis is suggestive of GABHS.
- Various rapid streptococcal tests claim differing levels of specificity and sensitivity.
  - Appear to be specific (95%–98%).
  - Sensitivity can be as low as 70%–85%.
  - Some cases of GABHS are not detected.
  - Positive rapid streptococcal test result is a sufficient indication to treat the patient.
- Culture should be sent if
  - Rapid test result is negative, but high index of suspicion exists that GABHS is the causative agent.
- Throat culture is not necessary
  - If little clinical evidence of pharyngitis or tonsillitis can be found in a child with sore throat
  - In patients with manifestations highly suggestive of viral infection
    - Coryza
    - Conjunctivitis
    - Cough
    - Hoarseness
    - Herpangina
    - Stomatitis
    - Sindbis virus
- Some individuals are *Streptococcus* carriers.
  - They may be found to be positive for *Streptococcus* infection during a viral illness.
  - An asymptomatic *Streptococcus* carrier does not need to be treated.
    - When symptoms are present, most physicians treat these individuals.
  - Difficult to ascertain that GABHS is not the cause of illness.
  - Performing pre- and post-illness rapid streptococcal tests or cultures on every child who presumably has GABHS pharyngitis is impractical.
    - All those who test positive are treated.

Serologic Tests

- If EBV infection is suspected, a heterophile antibody or specific EBV test can be ordered.
  - Ascertain with the reference laboratory whether an immunoglobulin G (IgG) or IgM test has been performed.
    - A positive heterophile test result may confirm only that children were exposed sometime in their life to EBV.
  - Tests of specific IgG and IgM antibody to various components of EBV are available.
    - Usually expensive and slow to produce results
    - Less-than-ideal tests to determine cause of acute pharyngitis
- Serologic tests exist to determine recent streptococcal infections.
  - Rarely helpful in evaluating for acute pharyngitis.
  - Antistreptolysin-O titer is used more commonly in diagnosing rheumatic fever.
    - Documents recent exposure to streptolysin with production of antibody

Leukocyte Count

- Only real value in performing is if infectious mononucleosis is suspected.
  - Patients with acute EBV infection tend to have relative lymphocytosis.
    - 10%–20% atypical lymphocytes
  - The leukocyte count may be a helpful diagnostic study.
    - Combine with heterophile or specific EBV antibody test for a child who has severe pharyngitis and is culture negative for GABHS.

TREATMENT APPROACH

- Pharyngitis caused by viruses generally is treated symptomatically with
  - Saline gargles
  - Throat lozenges
  - Analgesics, such as acetaminophen
- When GABHS has been documented, by positive rapid *Streptococcus* test result or by culture, antibiotics are indicated primarily to prevent subsequent development of rheumatic fever.
  - Early antibiotic treatment will shorten duration and severity of symptoms by 24–36 hours.
  - Patients should be kept out of school and avoid close contact with family and friends for only 24 hours.
    - Numerous studies have shown that they have negative culture results after just 24 hours of antibiotic therapy.
- Controversy exists over whether to begin antibiotics for presumptive GABHS pharyngitis while waiting for culture results.
  - Rheumatic fever can be prevented even if treatment is started as late as the ninth day of symptoms.
  - The decision to begin therapy immediately rests with the individual physician who knows the circumstances.

SPECIFIC TREATMENTS

Antibiotic Therapy

GABHS

- The presence of GABHS mandates early antimicrobial therapy.
  - Start within 9 days of onset of symptoms.
- Various antibiotic regimens have been used for GABHS pharyngitis or tonsillitis.
  - Standard therapy has been a 10-day oral course of potassium penicillin or amoxicillin given 2 or 3 times a day.
  - Alternatively, intramuscular benzathine penicillin G may be given as a single injection.
    - These injections are often painful, not only initially but also for a few days afterward.
  - Patients allergic to penicillin may be given
    - Erythromycin or a cephalosporin for 10 days
    or
    - Azithromycin for 5 days
  - Shorter courses of newer antibiotics have been studied and shown to be effective in eradicating GABHS from the pharynx.
    - Their efficacy in preventing rheumatic fever is not clear, although presumed.
- Cephalosporins have been shown to be superior to penicillin in eradicating GABHS from pharynx.

Other Bacteria

- Gonococcal pharyngitis.
  - One intramuscular injection of ceftriaxone is recommended.
  - In young children with this diagnosis, sexual abuse must be investigated.

- *A haemolyticum.*
  - Clarithromycin
  - Erythromycin
  - Azithromycin
- Other possible bacterial causes of pharyngitis are treated with appropriate antibiotics once the causative organism has been determined.

Corticosteroids

- Administration of corticosteroids to decrease pain in acute exudative pharyngitis has been studied in adults and found to provide some benefit.
- Use in children is not recommended.
  - Except in rare situations, such as infectious mononucleosis infection with imminent airway obstruction

Tonsillectomy

- Parents often raise the question of tonsillectomy after a child has multiple episodes of pharyngitis or tonsillitis.
  - Tonsillectomy is not indicated in children with recurrent pharyngitis except
    - In cases of documented recurrent, frequent streptococcal infection
    - In those who develop a peritonsillar abscess

WHEN TO ADMIT

- Toxic appearance (suspected toxic shock syndrome)
- Peritonsillar abscess
- Retropharyngeal abscess
- Acute rheumatic fever

WHEN TO REFER

- Suspected peritonsillar abscess
- Suspected retropharyngeal abscess
- Recurrent GABHS (5 episodes in 1 year) for tonsillectomy

FOLLOW-UP

- The physician must be aware of the possibility of a peritonsillar or retropharyngeal abscess or cellulitis.
  - Should reexamine the throat of any patient who is not improving.

COMPLICATIONS

- Most cases of pharyngitis present no unusual complications.
  - Many are viral.
  - Resolve with or without therapy.
- Acute tonsillopharyngitis may progress to a peritonsillar abscess.
  - Infection begins with the typical signs and symptoms of pharyngitis, such as
    - Sore throat
    - Dysphagia
    - Fever
  - Usually in an older child who often has a history of recurrent tonsillitis.
  - Systemic symptoms may develop.
    - Malaise
    - Poor appetite
    - Chills
    - Mild dehydration
  - Symptoms progress rapidly to more severe pharyngeal symptoms.
    - Difficulty swallowing and speaking.
    - The child has a toxic appearance.
    - Trismus almost always occurs.
  - The characteristic signs are
    - Muffled (hot potato) voice, trismus, and major leukocytosis
  - Needle aspiration can be performed only if the abscess is within the superior pole.
    - The success rate of needle aspiration compares favorably with that of incision and drainage in these types of cases.
  - Computed tomography and intraoral ultrasonography are quite reliable in distinguishing abscesses from cellulitis alone.
  - Initial antimicrobial therapy is clindamycin *plus* a third-generation cephalosporin, such as
    - Ceftriaxone
    - Cefotaxime
    - Ceftazidime
  - Routine tonsillectomy along with or after medical management is recommended.
- Other suppurative complications can also develop, such as
  - Cervical adenitis
  - Acute otitis media
  - Sinusitis
  - Pneumonia
- Hematogenous spread of a bacterial organism is possible, which can result in
  - Bacteremia
  - Joint, bone, or meningeal infection
- Rheumatic fever is the major complication of streptococcal pharyngitis.
  - Can be life-threatening.

- Occurs sometime after the acute throat infection.
- The incidence of rheumatic fever is low in North America.
  - Still occurs and has been seen in increasing numbers

- Acute glomerulonephritis is possible after streptococcal throat infections.
  - Much more likely after streptococcal skin infections
- Some evidence has shown association between GABHS infection and obsessive-compulsive disorders and tic behavior in children.
  - This clinical entity is termed *pediatric autoimmune neuropsychiatric disorder associated with group A streptococcal infection* (PANDAS).
  - Documentation is largely anecdotal.
    - Includes the observation that these children have high concentrations of antibody to streptococcal antigens
  - Small series have noted improvement in obsessive-compulsive disorder behavior or tics when these children are GABHS positive and treated with penicillin.
  - Many still question the authenticity of PANDAS.

PREVENTION

- History of parental smoking should be sought.
  - If history exists, advise measures to reduce the child's exposure to cigarette smoke.

DEFINITION

- *Phimosis:* nonretractile foreskin, physiologic or pathologic

SIGNS AND SYMPTOMS

Phimosis

- Can be physiologic or pathologic.
- At birth, most boys have physiologic phimosis.
  - Inner surface of the foreskin is developmentally fused to the glans penis.
- Over time, desquamation and glandular secretions allow gradual separation of the foreskin.
- Smegma.
  - The epithelial debris generated during desquamation
  - Sometimes can be seen under the foreskin as pearls
    - Requires no intervention
- Accumulations are released as the foreskin becomes more retractile.
  - May be mistaken for infection
- Retractability increases yearly.
  - By 1 year of age, 50% of uncircumcised boys have retractile foreskins.
  - By 3 years, 90%.
  - By 6–7 years, 92%.
  - By adolescence, 99%.
- Lack of clear diagnostic criteria makes it difficult to distinguish pathologic from physiologic phimosis.
  - *Physiologic phimosis* is described as unretractile foreskin that is supple and unscarred.
    - On attempted retraction, foreskin lies flat against the penis and is effaced.
    - Tip opens as a flower.
    - Young boys may exhibit preputial adhesions where part of the foreskin does not completely retract.
    - No visible constricting ring.
    - Not pathologic.
    - Resolves on its own.
  - In *pathologic phimosis,* margin between foreskin and glans is rolled and thickened.
- Balanitis xerotica obliterans (BXO)
  - Histologically resembles lichen sclerosus et atrophicus.
  - Severe phimosis can be a significant complication in boys receiving hematopoietic stem cell transplantation.

Paraphimosis

- Occurs when the foreskin is retracted, is not replaced immediately, and becomes trapped behind the corona.
  - May happen during cleaning
  - May occur during procedures such as catheterization
- Fibrous ring at the base of the corona causes venous congestion.
  - Leads to
    - Extreme penile pain
    - Swelling of the glans with a collar of swollen foreskin at the coronal sulcus

Balanitis or Balanoposthitis

- Characterized by
  - Erythema
  - Edema of prepuce that produces purulent discharge from the preputial orifice
    - Edema can involve some of the penile shaft.
- Patients may complain of dysuria.
- Condition usually occurs when the prepuce is wholly or partially retractable.

LABORATORY FINDINGS

- Sexually transmitted infections
  - Appropriate diagnostic tests (DNA probes) should be obtained.

TREATMENT APPROACH

- Treatment approach depends on whether the phimosis is thought to be physiologic or pathologic.
  - Watchful waiting results in resolution of most cases of physiologic phimosis.
  - Treatment alternatives if child is believed to have pathologic phimosis include
    - Topical corticosteroid cream
    - Surgery
- Choice regarding which patients should be referred and receive therapy may be unclear.
- Little agreement exists in the literature.
- Circumcision should be undertaken for
  - BXO
  - Phimosis resistant to corticosteroid therapy
  - Voiding problems
  - Recurrent balanitis
  - Urinary tract infections
- Ballooning of the foreskin during micturition is not, by itself, a reason for circumcision.
- Most cases of phimosis probably are physiologic and will resolve spontaneously over time.

- Some urologists question whether true phimosis can exist before age 5 and question whether any treatment need be initiated.
- Others use the age of 3 years as an upper limit and initiate a trial of corticosteroid creams (if no indication for surgery) at that time.
- Argument in favor of treating children who are younger (>3 but <5 or 6 years).
  - Most noninvasive therapy (topical corticosteroids) is more successful in younger children than older children.
  - Compliance is greater at that age because parents are able to apply the cream.
  - When older children become responsible for cream application, compliance and success decrease.

SPECIFIC TREATMENTS

Phimosis

- Topical corticosteroid creams
  - Multiple studies have investigated the use of topical corticosteroid creams.
  - 4- to 8-week course of therapy has been found to be ~85% effective.
  - High-potency corticosteroid creams, such as 0.05% betamethasone, have been studied the most.
  - Medium-potency topical corticosteroid (ie, clobetasone butyrate 0.05%, fluticasone propionate 0.05%, and triamcinolone acetonide 0.1%) has been shown to have similar resolution rates.
    - Lower-strength corticosteroid may be an option.
  - Creams are applied to the tip of the prepuce and down to its junction with the glans.
    - Twice a day for 4–8 weeks
  - Application of creams should be accompanied by gentle retraction of the foreskin.
  - To prevent the incidence of recurrence, gentle retraction of the foreskin with cleaning should continue after the cream is discontinued.
  - Corticosteroids are believed to be therapeutic by
    - Decreasing any potential inflammation between the foreskin and glans
    - Thinning the skin, making it more supple
  - Topical corticosteroid therapy has multiple advantages over more traditional surgical management.
    - Less invasive.
    - Avoids risks of surgery: bleeding, deformity, meatal stenosis.
    - No anesthesia risks.
    - Cost-effective—25% the cost of surgery.
    - Preservation of prepuce may be desired for social and cultural reasons.
    - Avoids potential emotional problems.
      - Some boys who undergo circumcision at an older age may develop severe emotional problems.
- Surgery
  - Surgical alternatives include dorsal slit surgery or circumcision.
  - Dorsal slit procedure involves making a single slit dorsally in the foreskin.
    - Preserves the prepuce.
    - Allows easy retraction of the foreskin.
    - Surgery is less involved than circumcision.
    - Cosmetic result is not as satisfactory as with circumcision.
    - Can be complicated by scarring.
  - Circumcision is more commonly used.
  - Beyond the neonatal period, surgery is usually done as an outpatient under general anesthesia.
    - In the postsurgical period, patients should be restricted from rough play or straddling toys for a couple of weeks.
    - To prevent adhesion to underwear or diaper, petroleum jelly or triple antibiotic ointment should be applied liberally to the newly exposed tip until it is well healed.
  - Forced premature retraction of the foreskin is *never* recommended.
    - May lead to significant adhesions and scarring
    - Painful
    - Traumatic

Paraphimosis

- Paraphimosis is a urologic emergency.
- Goal of treatment is to replace the foreskin in its normal position.
  - In early stages, the foreskin may be replaceable manually without sedation.
  - As condition progresses, anesthesia may be required.
    - Penile block
    - Sedation
    - General anesthesia
- Gentle persistent pressure is used to decrease edema and allow reduction of foreskin.
  - In infants and children, allowing an application of 2.5% topical lidocaine to take effect may allow manual reduction to be more successful.

- Sometimes, to relieve swelling
  - — Incision must be made in the fibrous ring.
  - — Multiple punctures must be made in the glans.

Balanoposthitis

- Local hygienic measures.
  - Sitz baths
  - Gentle cleaning
  - 1% hydrocortisone cream
- If irritation does not resolve, treatment with antimicrobials may be necessary.
- Circumcision usually is considered only for recurrent episodes.

WHEN TO ADMIT

- Paraphimosis
  - Failure of manual reduction with vascular compromise of the glans
- Balanoposthitis
  - Swelling of the penis with redness and streaking
  - Systemic infection or sepsis
  - Inability to urinate
  - Vascular compromise of the glans

WHEN TO REFER

- Phimosis
  - Obvious or suspected penile deformities.
  - Failure of topical corticosteroids.
  - BXO.
  - Parents desire circumcision.
  - Association with urinary tract abnormalities/obstructive uropathy.
- Paraphimosis
  - Failure of manual reduction
- Balanoposthitis
  - Recurrent episodes

COMPLICATIONS

- Paraphimosis
  - If no treatment is initiated, ischemia and necrosis of the glans can result.

DEFINITION

- Comprises the triad of micrognathia, glossoptosis, and obstructive apnea
  - *Micrognathia:* shortening and narrowing of the mandible and chin.
  - *Glossoptosis:* posterior displacement of the tongue into the pharynx.
  - *Airway obstruction:* caused by glossoptosis and often affects breathing and feeding.
  - Cleft palate is often associated with glossoptosis and micrognathia.
    - Cleft palate can be U-shaped or V-shaped and can involve the soft palate, hard palate, or both.
- Formerly known as Pierre Robin syndrome

SIGNS AND SYMPTOMS

- Suspected when a neonate feeds poorly or cannot maintain oxygen saturation
- Obstructive apnea
  - Most critical problem
  - Sometimes become evident only later in infancy
  - Mildest end of the spectrum
    - Little or no evidence of respiratory difficulty
    - Increased caloric expenditure and early fatigue with feeding owing to decreased respiratory reserves
    - Inadequate weight gain
    - Most readily confirmed with polysomnogram showing frequent obstructive events with or without oxygen desaturation

DIFFERENTIAL DIAGNOSIS

- Unlike laryngomalacia, micrognathia may lead to obstruction with inspiration and expiration on an endoscopic examination.

DIAGNOSTIC APPROACH

- Clinical diagnosis.
- No universally accepted tests or imaging studies to diagnose micrognathia or retrognathia.
- If a genetic syndrome related to micrognathia is suspected, testing for the genetic condition may be available.
- If Pierre Robin sequence is suspected, prompt clinical evaluation is crucial because obstructive apnea can lead to long-term complications.
- Comprehensive evaluation should be done by
  - Pediatric otolaryngologist
  - Pulmonologist
  - Speech therapist
  - Anesthesiologist
  - Craniofacial surgeon
  - Geneticist
- Initial evaluation should include a family history focusing on individuals with Pierre Robin sequence or cleft palate, suggesting a genetic cause.
- Family members with high myopia or a detached retina suggest Stickler syndrome (hereditary progressive arthro-ophthalmopathy).
- If apnea spells are suspected, the airway should be examined closely, likely with nasoendoscopy by an otolaryngologist and bronchoscopy by a pulmonologist.
- Analyze the position of the tongue and evaluate for any lower airway disease.

LABORATORY FINDINGS

- Consider genetic testing after initial evaluation.
  - Neurologic findings or malformations unrelated to the micrognathia
  - If growth and feeding abnormalities persist after airway obstruction has been addressed
- DNA microarray, which is more sensitive than chromosome analysis, can identify chromosomal microdeletions and micro-duplications linked to multiple congenital anomaly syndromes.
- Fluorescence in situ hybridization analysis can identify deletion 22q11.2, a common cause of Pierre Robin sequence.
  - This technique is not a screening tool because it tests only for the specific disease in question.

IMAGING

- Prenatal diagnosis is not always possible, but advances in prenatal imaging and the availability of high-resolution and 3-dimensional ultrasound make severe cases of micrognathia identifiable in the fetus.
  - Useful because these neonates may require intubation in the delivery room.
- Polysomnography evaluates apnea spells during sleep in various positions; pulse oximetry alone is not sensitive enough.
  - Place the neonate in a prone position.
  - Gravity will pull the tongue forward, often relieving the glossoptosis and creating an open airway.
- 3-dimensional computed tomography maps out the bony anatomy, should surgical interventions be needed.
- Barium swallow study with speech evaluation is used to evaluate feeding and respiratory dynamics while patient is awake and during feeding.

TREATMENT APPROACH

- Prenatal management.
  - Delivery in a hospital with a neonatal intensive care unit
  - Evaluation by a neonatologist with immediate access to an airway specialist
  - Extreme cases: may be desirable to have an otolaryngologist immediately available
- Neonate identified prenatally with severe micrognathia may need immediate intubation after delivery.
- Others may simply require monitoring for episodes of apnea, decreased oxygenation, and poor feeding.
- No intervention needed for neonate who has no episodes of desaturation and gains weight.
- Further evaluation and management needed for neonates who
  - Have apnea episodes.
  - Have oxygen desaturations.
  - Cannot feed without desaturation.
  - Do not gain weight.

SPECIFIC TREATMENTS

Nonsurgical

- About half of neonates with Pierre Robin sequence can be managed nonsurgically.
- Initial approach when Pierre Robin sequence is suspected.
  - Polysomnogram is normal or mildly abnormal with few apnea spells: Positioning and supplemental oxygen through nasal cannula may be the only intervention required.
  - Polysomnogram shows moderate to severe abnormalities: A nasopharyngeal airway can be placed while further treatments are considered.
- Feeding interventions.
  - Position the neonate on his or her side or semi-reclined during feeding to alleviate respiratory distress.
  - If ineffective, a speech therapist or occupational therapist should evaluate the neonate to optimize feeding technique.
  - Breastfeeding.
    - Usually requires consultation with an experienced lactation specialist; almost always results in use of pumping and bottle-feeding.
    - Closely monitor weight gain and apnea spells.
    - Some mothers can breastfeed after distraction if they are still lactating and there is no cleft.
  - When a cleft palate is present, a special bottle should be used with compressibility, allowing the milk to be squeezed into the neonate's mouth.
    - Haberman Feeder
    - Pigeon Cleft Palate Nurser
    - Mead Johnson Cleft Lip/Palate Nurser
  - Often, a nasogastric tube must be placed for adequate caloric intake, especially during mandibular distraction.
  - Oral feeding often improves significantly after mandibular distraction.
  - Gastrostomy tube.
    - Required for neonates with severe neurologic deficits and high risk for aspiration
    - Must be considered if intake does not improve after mandibular distraction

Surgical

- Surgical interventions for apnea spells depend on severity and take into account the entire clinical picture.
- Tracheostomy.
  - Historically, the primary option for severe, persistent obstruction
  - Still performed for airway obstruction, chronic cardiopulmonary disease, and neurologic compromise
  - Required only in a small subgroup
    - To prevent aspiration and other complications if neonate has evidence of neurologic impairment
    - If there is an underlying genetic syndrome with many organ systems involved, such as cardiac and pulmonary
    - If other airway management options have failed
- Mandibular distraction.
  - Primary treatment to avoid tracheostomy and associated complications, increased mortality rate, and delayed speech development.
    - Goal is to bring the base of the tongue forward, relieving the glossoptosis and apnea.
  - Distraction devices can be used on multiple planes of a bone and can be placed internally or externally.
  - Current options are usually not associated with severe scarring.
  - Technique slowly elongates the mandible by bilateral corticotomies (partial fractures) with placement of percutaneous wires and distraction devices.

- After the latency period of 24–48 hours, the distractor is turned daily to achieve about 1–4 mm of distraction per day.
- Stable neonates can sometimes be taken home after parents are taught to manipulate the distractor device.
- On average, involves 2–4 weeks of active distraction and another 4–6 weeks for bone consolidation.
- During the distraction period, neonates are often fed through a nasogastric tube.
  - — Some facilities allow oral feeding during distraction, but this is not the standard practice.
- New techniques for distraction osteogenesis include miniaturized and absorbable distractor plates.
- Although many children are distracted at a young age (infancy to 3 years), many undergo distraction at 6–7 years if airway issues permit.

- Tongue-lip adhesion.
  - Older technique that sutures the tongue base to the anterior mandible.
  - Abandoned by most surgeons because of the adverse effects.
    - — Aspiration
    - — Feeding abnormalities
    - — Speech delay
    - — Subsequent tongue atrophy and weakness
  - <15% of pediatric centers report using this technique.

WHEN TO ADMIT

- Poor weight gain in the first week of life
- Stridor or other respiratory symptoms on examination (or by history)
- Suspicion of other malformations or neurologic abnormalities, requiring further evaluation by specialists

WHEN TO REFER

- There should be a low threshold for involving a geneticist with any case of Pierre Robin sequence to identify these high-risk neonates.
- Apply a team approach for these neonates because a single solution cannot be broadly applied.
- Craniofacial management is expected.
- A surgical intervention or assessment is likely (ie, for airway or feeding).
- Poor feeding or respiratory distress in neonates.

COMPLICATIONS

- Long-term consequences of airway compromise
  - Hypoxia
  - Failure to thrive
  - Dehydration
  - Electrolyte imbalance
  - Cor pulmonale
  - Death
- Problems with breastfeeding and bottle-feeding, usually secondary to airway obstruction
  - Suck-swallow-breathe coordination can be very difficult in neonates with micrognathia and glossoptosis.
  - If neonate has cleft palate, feeding is further compromised because suction cannot be generated for feeding.
  - Increased risk of aspiration of formula or human milk.
  - If Pierre Robin sequence is part of an associated syndrome, feeding problems and weight gain may be further compromised.
- Mandibular distraction osteogenesis
  - Bone malunion or malalignment requiring repeat distraction
  - Potential disturbance of mandibular growth at the temporomandibular joint
  - Injury of facial nerve
  - Tooth loss or damage to underlying tooth buds
  - Infection of skin where the distractor inserts if skin is not properly cleaned
- Tracheostomy (all related to chronic foreign body in airway)
  - Dislodgement or occlusion of the tube
  - Buildup of granulation tissue
  - Delayed speech
  - Recurrent infections

PROGNOSIS

- With prompt identification of isolated Pierre Robin sequence in a neonate who demonstrates respiratory distress, the condition should not affect life span.
- Neonates with isolated Pierre Robin sequence and those with Stickler syndrome (>50% of cases) should have normal cognition, good growth, and a normal life span.
- Increased risk for long-term morbidity and mortality because of the risks inherent to the specific syndrome.

DEFINITION

- Pinworm is a condition caused by an infestation with *Enterobius vermicularis.*

SIGNS AND SYMPTOMS

- One-third or more of infestations are asymptomatic.
- Signs and symptoms include
  - Localized perianal pruritus (most commonly reported symptom)
  - Restlessness
  - Fitful sleep
  - Secondary excoriation
  - Dermatitis
  - Genitourinary symptoms
    - Migrating pinworms may enter the vagina or urinary tract in female patients.
  - Granulomatous reaction (rare)
    - Granulomas-containing worms have been an incidental finding in the
      - Gut
      - Vulva
      - Cervix
      - Fallopian tubes
      - Peritoneum
      - Bladder
  - Appendicitis and eosinophilic colitis (rare)
    - Inflammation associated with the parasite has been found in these conditions.
    - Lack of abdominal symptoms supports the notion of minimal gastrointestinal abnormality with this parasite.

DIAGNOSTIC APPROACH

- Diagnosis is dependent on identifying adult worms or eggs.
- Eggs are seldom found in feces even using concentration techniques.
- The best way to make a diagnosis is to use the cellophane tape technique.

LABORATORY FINDINGS

- Cellophane tape technique to visualize pinworm eggs
  - When the child awakens in the morning, press the adhesive side of a 2-inch strip of clear cellophane tape against the perianal skin using a tongue depressor.
    - Commercially produced kits are available for this purpose.
  - Tape is then placed on a microscope slide with the adhesive side down.
    - Eggs are naturally transparent.
    - Staining with lactophenol cotton blue enhances detection.
  - A single test should detect ≥50% of infestations.
    - 3 will detect 90%.
    - 5 will detect virtually 100%.

TREATMENT APPROACH

- Eradication is extremely difficult because of
  - Ubiquity, infectivity, and persistence of the parasite
  - High level of infestation in symptomatic patients
- Vigorous pursuit of a permanent cure may provoke needless turmoil and anxiety in the family.
- The most important aspects of treatment are
  - Humility on the part of the physician
  - Reassurance of the family

SPECIFIC TREATMENTS

Pharmacologic Treatment

- Reasonable to treat a confirmed individual patient or the entire family.
  - Single dose of mebendazole (100 mg for all ages) or albendazole (400 mg for all ages)
    - Extremely effective and has virtually no side effects
  - Pyrantel pamoate administered as a single dose of 11 mg/kg (maximum 1 g)
    - Effective
    - Transient headache and abdominal symptoms have been reported.
- Treatments are effective against adult worms only.
  - Therapy is usually repeated in 2 weeks to eradicate emerging parasites.

General Measures

- Clipping the fingernails (a repository for eggs)
- Frequent hand washing
- Daily morning showers
- Tight-fitting cotton underpants
- Bland ointment (eg, petroleum jelly) applied to the perianal region to limit dispersal of eggs
- Cleaning floors in sleeping areas thoroughly, particularly in cases of recurrence
- Washing clothing and bedding at the time of treatment

DEFINITION

- *Plagiocephaly* means "oblique head" (Greek origin).
  - Term is used to describe any abnormality in the shape of the head, irrespective of its cause.
- Posterior deformational plagiocephaly (PDP) is a condition in which flattening of the occiput occurs as a result of mechanical factors that affect the malleable growing skull in utero or during early infancy.
  - Also referred to as *benign positional molding, posterior plagiocephaly,* and *occipital plagiocephaly*

SIGNS AND SYMPTOMS

- PDP is first noticed by parents and health care professionals when the infant is 2–3 months of age.
- Severity peaks at 4 months and then resolves gradually over time.
- Infants with PDP exhibit preferential head position and turn the head only to one side.
- When head is viewed from above
  - Frontal prominence is observed on the same side as the occipital flattening.
  - Ear on that side is anterior as compared with the other ear.
- Other craniofacial abnormalities that may be observed on the affected side include
  - Prominent mandibular sulcus with mandibular tilt.
  - Uplifted lower helix.
  - Smaller ear.
  - Unilateral epicanthal fold.
  - Most have one-sided occipital bald spots.

DIFFERENTIAL DIAGNOSIS

- Distinguishing lambdoid synostosis from PDP in infants with flat posterior plagiocephaly is critical because of differences in management.
  - Rarely, clinical differentiation between them may be difficult.
- Lambdoid synostosis is a rare condition that occurs in ~2% of all cases of craniosynostosis.
  - Head is trapezoid shaped.
  - Ear is displaced inferiorly and posteriorly.
  - Posterior basal skull is tilted, with prominence of mastoid process present on the same side.
  - Facial deformity is absent or minimal.
- PDP.
  - Head is shaped like a parallelogram.
  - Significantly greater protrusion of the forehead on the same side of the occipital flattening than with lambdoid synostosis.
  - Ear on flattened side is displaced anteriorly.
  - Facial deformity.
- Presence of torticollis must be ruled out in every case of flattened occiput because of its greater association with PDP.
  - Primary care physician should perform passive and active head rotations and check for tightness of the sternocleidomastoid muscle.
  - Eye on the side of torticollis appears to be incompletely open as a result of the vertical displacement of soft tissues of the cheek.
  - Mothers of infants with torticollis note that they have difficulty feeding the infant from both breasts because the infants have trouble turning their heads.

DIAGNOSTIC APPROACH

- Diagnosis of PDP in infancy is made primarily based on history and physical examination.
- If the infant has a normal, rounded head at birth and after a few weeks or months develops an occipital flattening, the most likely diagnosis is PDP.

IMAGING

- Imaging studies usually are not required.
- In the past, skull radiographs were used to rule out lambdoid suture synostosis.
  - Ultrasound examination of the lambdoid suture also has been shown to be useful in ruling out lambdoid suture synostosis.
- Computed tomography scans are sensitive in diagnosing synostotic plagiocephaly.
  - 3-D scans are helpful, but 2-D axial views are more sensitive in assessing suture patency.

TREATMENT APPROACH

- Early recognition and intervention improves outcome.
  - If not treated appropriately, quality of life may be reduced.
- In most patients, the head shape improves with changes in head position or helmet therapy.
- Definitive treatment guidelines have not been developed.
- Early treatment is successful in most cases of mild to moderate PDP.
- Treatment started >12 months does not produce significant benefits.

SPECIFIC TREATMENTS

Initial Management

- Early treatment is similar to preventive measures.
- Educate parents about changing the infant's head position frequently.

Neck Motion Exercises

- If the infant is found to have torticollis, parents should be taught neck motion exercises to use with the baby.
  - First exercise is used to stretch the sternocleidomastoid muscle.
    - Place one hand on the infant's upper chest.
    - Rotate infant's neck with the other hand so chin touches the shoulder.
    - Hold infant's head in this position for 10 seconds.
    - Then rotate head to the other side and hold in that position for an additional 10 seconds.
  - Second exercise stretches the trapezius muscle.
    - Infant's head is tilted so the ear touches the shoulder and is held in that position for 10 seconds.
    - Same process is followed on the other side.
- Parents should perform these neck exercises with every diaper change, with 3 repetitions of each exercise.
  - ~2 additional minutes per diaper change are required for these exercises.
- Infant should be referred for physical therapy for stretching exercises if these exercises fail to improve torticollis within 2–3 months.
- If no improvement is evident, or if plagiocephaly worsens after 2 months of repositioning and physical therapy, refer infant to a pediatric neurosurgeon or craniofacial surgeon.

Helmets

- Skull-molding helmets have been used for reshaping the affected skull.
- Must be used in the age range of 4–12 months because of the malleability of the infant's skull during this period.
- Ideally, therapy is begun at 4–6 months of age; may be continued until 12–14 months of age.
- Head growth remains typical during helmet therapy; helmet works by symmetrically shaping the cranial growth.
- Use of helmets is more beneficial for
  - Patients with severe deformity
  - Infants with mild to moderate severity who are resistant to position changes and physical therapy
- No consensus exists on use of helmets.
- Disagreement exists on cost-effectiveness of helmets.
- American Academy of Pediatrics (AAP) states that helmets are beneficial in the treatment of PDP after position changes and exercise have failed.
- Helmets used for treating PDP are considered to be class II neurologic devices and are regulated by the US Food and Drug Administration.
- Information on the approved orthotics can be obtained at www.fda.gov.
- Recently, Dutch researchers used 3-D whole-head surface scans to compare infants with deformational plagiocephaly who were treated with helmets or active repositioning.
  - The helmeted group had significantly greater reduction in asymmetry than the repositioned infants (maximum reductions, 4.0% vs 2.5%; mean, 0.9% vs 0.5%).
- In New Zealand, comparison of head shape and neurodevelopmental outcomes during infancy and at a mean age of 4 years.
  - PDP improved or normalized in 87% of children by age 4 years without use of a helmet.
  - Parental concerns about head shape and assessment of development improved.

Surgery

- Rarely needed.
- May be indicated in severe cases in which infants have presented late for management by repositioning, physical therapy, or helmet therapy.
- Craniotomy does not provide superior results as far as a cosmetic outcome is considered.
- Associated with significant morbidity.

WHEN TO ADMIT

- Surgical correction of PDP.

WHEN TO REFER

- After position change and physical therapy have failed to correct PDP
- In severe cases
- When the patient who has PDP is >12 months
- When lambdoidal craniosynostosis is a possibility

COMPLICATIONS

- Uncorrected or improperly treated PDP can lead to marked psychosocial developmental sequelae.

PROGNOSIS

- In two-thirds of cases, PDP resolves by 2–3 years of age.
- Resolution is slow in children with limited head rotation and low activity level.
- In most cases, early implementation of repositioning and neck exercises yields considerable response over a 2- to 3-month period.
- The ipsilateral temporomandibular joint is pushed anteriorly in patients with PDP, and the mandible develops asymmetrically.
  - Positional and helmet therapy improve head shape but not the position of the temporomandibular joint or the asymmetry of the mandible.
- PDP causes forehead and facial shifts that may lead to asymmetric positioning of eyes and bilateral astigmatism.
  - Fitting corrective glasses on an asymmetric head is difficult.
- Cognitive and psychomotor development have been observed to be mildly delayed in patients with PDP.
  - Whether delays can be corrected with therapy is not known.
  - Whether delays are the cause or the effect of PDP is not known.
  - Long-term follow-up of patients with PDP has shown persistence of developmental delay.
  - Decreased prone positioning may be the main factor associated with mild motor delay.
  - Large prospective short-term outcome studies show motor delays, but long-term outcome studies have inconsistent findings.

PREVENTION

- In most infants, PDP can be prevented by
  - Alternating supine head position during sleep
  - Periodically changing position of the crib to require the child to look away from the flattened side to see parents or a light source
- The AAP has recommended a certain amount of prone positioning, or *tummy time,* while the infant is awake and being observed.
  - May help prevent development of flat occiput.
  - May facilitate development of upper shoulder girdle strength for timely attainment of certain motor milestones.
  - Theories suggest that prone position prevents PDP by correcting or preventing infants' positional preferences.
- Parents and health care professionals should be educated on different techniques to reduce the risk for development of PDP.
  - Caregivers should be encouraged to
    - Change the head position of a sick newborn whenever possible.
    - Provide care from alternate sides of the crib.
    - Reposition the infant from head to foot periodically.
- Breastfed infants are less likely to develop PDP because alternate head positioning is promoted.
  - Parents should be advised to use alternate arms during each bottle-feeding.

DEFINITION

- Community-acquired pneumonia (CAP) is acquired outside the hospital environment.
- Nosocomial pneumonia is acquired in the hospital environment.
- The World Health Organization has defined pneumonia on the basis of clinical findings because chest radiology is not readily accessible in many parts of the world.
- The pathology of pneumonia is described as lobar, bronchopneumonia, interstitial, or miliary.

SIGNS AND SYMPTOMS

Signs and Symptoms That Suggest the Diagnosis

- The microbiologic diagnosis of pneumonia is difficult to prove in many cases without extensive investigation.
  - It is helpful to be aware of which organisms are in the community at the time.
- The age of the child will suggest the most likely cause (**Table 1**).
- Infant to school age (1–4 years).
  - After 1 month of age, cough is the most common presentation.
  - Fever.
    - Significant fever is usually present in bacterial pneumonia.
    - In viral or atypical infections fever may be low grade.
    - However, height of fever is a poor indicator of etiology.
  - Respiratory syncytial virus (RSV) is the most common pathogen.
    - In children >2 years, RSV does not cause lower respiratory tract infection except in immunocompromised (especially transplant) patients.
  - Parainfluenza type 3 occurs year-round, with peaks in the spring.
  - Types 1 and 2 are typically seen in the fall.
- 5 years of age to adolescence.
  - The most common presentation is cough and fever, which is very nonspecific.
  - The appearance of the child will aid in arriving at the diagnosis of pneumonia.
    - Signs of respiratory distress, including retractions and nasal flaring
    - Abnormal auscultation

Bacterial

- Pneumococcal pneumonia
  - May be preceded by a mild upper respiratory infection (URI).
  - Examination of the chest may not be abnormal in the infant and young child.

Table 1. Signs and Symptoms of Pneumonia by Age

	≤2 mo	2–12 mo	1–5 y	>5 y
Respiratory rate WHO threshold	≥60/min	≥50/min	≥40/min	≥30/min
Symptoms and signs	Cough Poor feeding Apnea Tachypnea Grunting Nasal flaring Retractions	Cough Fever Poor feeding Tachypnea Grunting Rhinorrhea Nasal flaring Retractions	Cough Fever Rhinorrhea Chest pain Tachypnea Retractions	Cough Fever Headache Pleuritic pain Abdominal pain Tachypnea Retractions
Auscultation	Crackles Wheeze	Crackles Wheeze	Crackles Wheeze Pleural rub	Crackles Wheeze Pleural rub

Abbreviation: WHO, World Health Organization.

P

- Infants may present with a sudden rise in body temperature, possibly a seizure, and diarrhea and vomiting.
- Cough may be absent, but evidence of respiratory distress includes tachypnea, nasal flaring, and perioral cyanosis.
- Friction rub is not often elicited.
- Older children
  - Usually present with fever, chills, dyspnea, and pleuritic chest pain.
  - May have sputum production, possibly with streaks of blood.
  - Crackles and dullness to percussion with bronchial breathing over the involved lobe are usual.
  - Abdominal pain, especially if the infiltrate(s) involves the lower lobe of either lung, is common.

■ Group A streptococcus (*Streptococcus pyogenes*)
- Uncommon.
- Clinical course is aggressive and may result in necrotizing pneumonia.
- Clinical appearance includes fever, chills, lethargy, cough, and dyspnea.

■ Staphylococcal pneumonia
- *Staphylococcus aureus* formerly was an uncommon cause of pneumonia in immunocompetent children, although it did occur in infants.
- A virulent strain of community-associated methicillin-resistant *S aureus* (MRSA) is now associated with life-threatening, complicated pneumonia.
- *S aureus* is more common after influenza and other viral URIs.
- Pneumonia results from inhalation of organisms or bacteremic spread.
- Clinical picture varies from a mild respiratory infection with fever, cough, and tachypnea to a rapidly progressive illness with dyspnea, cyanosis, and septic shock.

■ *Pseudomonas aeruginosa*
- Rarely causes pneumonia in healthy children.
- *Pseudomonas* species is a common complication of patients with endotracheal tubes or tracheostomy.
- The dominant organism in cystic fibrosis (CF).
- Occurs more often in immunosuppressed children or those with poorly controlled HIV infection, neutropenia, and complement deficiency.
- The most common cause of pneumonia in the intensive care environment.
- Reported following exposure in hot tub spas.
- Sputum produced typically is green.
- Pleural effusion is common, and pneumonia may have a lobar or diffuse bilateral bronchopneumonia radiographic pattern.

■ *Klebsiella pneumoniae*
- Acute onset with fever and chills.
- Productive cough yielding abundant thick sputum that is typically blood-tinged ("red currant jelly sputum").
- Abscess formation, cavitation, and empyema are common.
- Infection is more commonly unilateral, typically in the upper lobes.

■ *Legionella pneumophila*
- Presents with fever, chills, and cough, which is initially nonproductive.
- Constitutional symptoms include headache, muscle ache, and, sometimes, ataxia (loss of coordination) and diarrhea or vomiting.
- Lung examination typically reveals crackles.

■ *Mycoplasma pneumoniae*
- Infection usually starts with a URI, with pharyngitis, cough, headache, and myalgias.
- Fever, if present, usually is <38.9°C (102.0°F).
- Cough.
  - Initially nonproductive
  - Can be severe and debilitating
  - May cause non-pleuritic chest pain
- Blood streaking of the sputum is not uncommon.
- In 5%–10% of children the URI progresses to bronchitis or pneumonia.
- Pleural effusion occurs in 5%–20%.
- Cutaneous manifestations include maculopapular rash and erythema nodosum.
- Extrapulmonary symptoms are not uncommon and include bullous myringitis.
- May be severe in sickle cell anemia.
  - Considered an important cause of acute chest syndrome
- Can be severe in Down syndrome, especially in children with congenital cardiac disease.
- Causes exacerbations of asthma in children and adolescents.
- Physical examination usually reveals oropharyngeal inflammation.
- Chest examination may be benign, with few crackles and rhonchi, even though a chest radiograph shows significant pneumonia.
- Wheezing, particularly in children with asthma.

- *Chlamydia trachomatis*
  - Most infants have a history of conjunctivitis, nasal stuffiness, and cough with tachypnea.
  - The infant with *C trachomatis* pneumonia is characteristically afebrile.
  - Chest examination reveals scattered crackles; wheezing is absent.
- *Chlamydophila psittaci* (ornithosis)
  - Difficult to diagnose.
  - May be more common than appreciated.
  - Most common disease is mild pneumonia, but more fulminant illness is possible.
  - Fever without elevation of the pulse.
  - Splenomegaly.
  - Blanching erythematous maculopapular rash.
  - Signs of hepatitis, disseminated intravascular coagulation, or meningoencephalitis.
- *Chlamydophila pneumoniae*
  - Initially there is a URI; many have no further symptoms.
  - Hoarseness and headache may be present.
  - Fever is uncommon.
  - Physical examination reveals crackles, wheezing, and rhonchi.
  - Even with treatment, tends to respond more slowly than mycoplasma.
  - Tends to recur if therapy is stopped too early.

Viral

- RSV
  - Infants tend to have less wheezing, less hyperinflation, and more crackles.
  - Clinically similar to bronchiolitis, with an upper respiratory prodrome followed by worsening cough and increasing respiratory distress.
  - Wheezing tends to be less prominent.
  - Crackles may be present.
- Influenza virus
  - Characteristic presentation
    - High fever
    - Chills
    - Muscle aches
    - Headache
  - Young children may have more nonspecific symptoms.
  - Starts as a URI with rhinitis, pharyngitis, and, initially, a nonproductive cough.
  - Young children may also have conjunctivitis and gastrointestinal symptoms and hypoxemia.
  - Secondary bacterial infection may occur.
- Human metapneumovirus
  - Similar to RSV, although illness tends to be milder and children tend to be older
  - Symptoms include rhinorrhea, cough, tachypnea, and fever.
  - Signs include retractions, crackles, and wheezing.
  - Clinically similar to RSV bronchiolitis, but pneumonia and respiratory failure may occur.
- Cytomegalovirus
  - A major cause of pneumonia in immunocompromised children, including those with transplant, HIV infection, and malignancy.
  - Typically, 2–3 months posttransplant, there are cough and fever, possibly leading to severe dyspnea and hypoxia.
  - Nonspecific symptoms.
  - The lung involvement is interstitial.
  - Pulmonary symptoms may be accompanied by gastrointestinal disease, especially diarrhea, and chorioretinitis.
  - May also occur in infants <3 months and be especially severe in preterm neonates.
- Herpes simplex virus
  - Also seen in immunocompromised and transplant patients.
    - Most at risk are those who are severely neutropenic or lymphopenic.
  - Difficult to diagnosis, and mortality can be high unless recognized early.
  - Acyclovir therapy and infectious diseases consultation is important.

Fungal

- Aspergillosis
  - 80%–90% of patients with acute invasive aspergillosis will have pulmonary disease.
  - Main symptoms are
    - Nonproductive cough
    - Fever
    - Shortness of breath
    - Blood in the sputum
    - Pleuritic chest pain
  - 25% may have minimal physical signs; others may present with hypoxemia.
  - Chronic invasive pulmonary aspergillosis is associated with diabetes mellitus, chronic granulomatous disease, and HIV.
- *Candida*
  - Fever, dyspnea, and evidence of sepsis.
  - Lung examination is variable, from noncontributory to rhonchi, crackles, and wheezing.

- Blastomycosis
  - Flu-like symptoms with fever, chills, night sweats, weight loss, and myalgia.
  - Pulmonary symptoms include cough and chest pain.
  - Acute and chronic forms.
    - Chronic form may last 2–6 months and is associated with weight loss and cough.
  - Acute or chronic pulmonary blastomycosis has the potential for a more severe course.
    - Life-threatening infection may disseminate to skin, central nervous system, and bone.
- Coccidioidomycosis
  - History of travel or residence in an endemic area.
    - Exposure can be as simple as driving through the area.
  - More than half of those infected are asymptomatic.
  - If there are symptoms, primary infection leads to a flu-like illness.
  - Symptoms include fever, dyspnea, arthritis, and rash.
    - The rash is characteristically erythema multiforme or erythema nodosum.
  - Primary infection may be followed by disseminated coccidioidomycosis, although less commonly in children than in adults.
  - Most recover even without treatment.
  - Some have fatigue that lasts for months.
- Histoplasmosis
  - Clinical features depend on size of the inoculum, immune status of the host, and presence of lung disease.
  - Exposure increases if there is major disturbance of soil, as with construction projects and proximity to chicken coops, especially those with rotten wood.
  - Incubation period is 9–17 days.
  - Acute illness is characterized by flu-like symptoms of fever, chills, muscle aches, nonproductive cough, and chest pain.
    - Acute symptoms may be mild (lasting <1 week) to severe (2–3 weeks).
  - Varied clinical manifestations, again differing with immune status.
  - Severe acute pulmonary syndrome results from exposure to a large inoculum and starts with an acute flu-like syndrome, with fever, chills, and myalgias.
  - Pulmonary symptoms develop with cough, dyspnea, and hypoxemia.
  - Chest examination includes diffuse fine crackles with, possibly, a pleural rub.
  - There may be rapid progression to acute respiratory distress syndrome.
  - Mediastinal obstructive syndrome results from hilar lymphadenopathy.
    - May be large enough to compress surrounding structures, including airway, great vessels, and esophagus.
- Pneumocystis pneumonia (PCP)
  - Symptoms and signs are nonspecific.
    - High index of suspicion is necessary in patients who are HIV infected or immunocompromised, especially if they are not taking prophylactic measures.
  - Symptoms typically are shortness of breath, fever, and nonproductive cough, with chills and weight loss.
  - Signs are tachypnea and tachycardia.
  - Auscultation may reveal some crackles, but, often, there are no adventitious signs.
  - The main finding supportive of the diagnosis is hypoxemia.

LABORATORY FINDINGS

General

- Complete blood cell count may reveal an elevated white cell count.
- Atypical lymphocytes may be found with viral infections, but the finding is nonspecific.
- In previously healthy children, it is not considered essential to attempt to find the etiologic agent.
- Pneumonia in children does not usually have bacteremia, and blood culture is not routinely required in immunocompetent children unless hospitalized.
  - If the child is critically ill or immunocompromised, blood culture result is more likely to be positive.
- Sputum culture, including Gram stain, and sensitivity may be considered in the older child.
- If the child does not respond to initial therapy in ≤72 hours or if there is a rapid progression of symptoms, further testing may be indicated.
- Elevation of C-reactive protein may predict more severe disease but does not differentiate bacterial from viral pneumonia.
- If the child has a pleural effusion and has not received antibiotics, a pleural tap should be considered.
  - If antibiotics have been given, the yield from pleural tap is low.
- Polymerase chain reaction (PCR), if available, may be helpful with further etiologic diagnosis.

Specific Pneumonias

- Pneumococcal pneumonia
  - Laboratory findings are not consistent.
  - White blood cell count >20,000/mL with clinical picture of pneumonia is indicative of pneumococcal disease.
    - Not recommended in the outpatient setting.
    - Yield from blood culture is low.
  - Sputum.
    - Finding of many polymorphonuclear leukocytes with gram-positive diplococci is almost diagnostic.
    - Young age is a barrier to sputum collection.
  - Antigen detection is not considered useful except for pleural fluid.
- *L pneumophila*
  - Blood test may reveal abnormal hepatic or renal function, and hyponatremia is common.
  - Detection of *L pneumophila* serogroup 1 is aided by detecting *Legionella* antigen in the urine.
- Mycoplasma
  - Mycoplasma immunoglobulin M (IgM) and IgG may be useful to confirm diagnosis, with sensitivity ~98% if both are done.
    - IgM may be negative in the first week of illness.
    - Presence of IgG may be indicative of past infection.
  - The specificity of *M pneumoniae* IgM detection during an outbreak is higher in those ≥19 years.
- Influenza virus
  - Positive A or B influenza virus can be determined by immunofluorescence or hemagglutination techniques.
  - PCR has higher sensitivity and specificity and is more readily clinically available, especially for hospitalized children.
- *Aspergillus*
  - Hyphae may be evident microscopically, but this does not prove diagnosis because other fungi may have a similar appearance.
  - Culture of sputum or bronchoalveolar lavage fluid.
    - Not definitive because specimens may be positive in those who are colonized with aspergillus.
    - Finding of galactomannan (GM) supports diagnosis of invasive aspergillosis.
      - Negative predictive value of GM is highly specific.
      - GM is not positive in 100% of patients with pulmonary aspergillosis.
      - GM test may be falsely positive in patients receiving piperacillin-tazobactam or ampicillin-sulbactam.
- Blastomycosis
  - Sputum is full of polymorphonuclear cells and has a high yield for fungal stain.
  - Fungus grows from culture of sputum, tracheal aspirate, bronchoalveolar lavage, cerebrospinal fluid, and urine.
  - Direct identification of the fungus is possible by experienced personnel.
  - Children who do not expectorate sputum may need bronchoscopy or lung biopsy to confirm diagnosis.
- Coccidioidomycosis
  - Coccidioidal IgM appears within 1–3 weeks of onset of symptoms and lasts for 3–4 months.
- Histoplasmosis
  - Rapid enzyme-linked immunoassays for *Histoplasma* antigen in urine, cerebrospinal fluid, and bronchoalveolar lavage fluid
  - Serology (immunodiffusion or complement fixation)
  - Cultures or tissue examination and stains
- PCP
  - Sputum
    - Expectorated sputum usually does not yield a satisfactory specimen.
    - Induced sputum production with hypertonic saline is the quickest way to make the diagnosis.
  - Bronchoalveolar lavage is the most common procedure performed.
  - Diagnosis is confirmed by various stains, including silver stains, which show the cysts.

IMAGING

General

- The standard imaging for diagnosis of pneumonia is a 2-view plain chest radiograph.
- Does not differentiate between viral and bacterial disease.
  - Lobar pneumonia, with disease restricted to the involved lobe, is more suspicious for bacterial pneumonia.
  - Perihilar scattered infiltrates, hyperinflation, and hilar adenopathy are more likely in viral pneumonia.
  - Round pneumonia, seen in younger children, is likely bacterial, particularly *Streptococcus pneumoniae,* but possibly *S aureus* and *Klebsiella* species.

- Ultrasound is increasingly being used to evaluate pulmonary problems and can assist in evaluation of lobar consolidation and pleural effusion.
- Computed tomography (CT) or ultrasound is indicated if there are complications.

Specific Pneumonias

- Pneumococcus
  - Chest radiograph
    - — May initially demonstrate lobar pattern and then extend beyond the lobar boundaries.
    - — The most common cause of "round pneumonia" pattern.
    - — Markings may be patchy or interstitial.
- Group A streptococcus
  - The most common radiographic pattern is a patchy bronchopneumonia.
  - In some there is lobar with progression to fibrinopurulent empyema.
- *S aureus*
  - Initial radiographic appearance is multiple nodular infiltrates, usually unilateral, which, in a few days, become cavitary; subsequently, pneumatoceles form.
  - Pneumothorax is common, especially in ventilated infants.
  - Empyema is present in most.
- *M pneumoniae*
  - Infiltrates are more likely to be bilateral than unilateral.
  - May be lobar, multifocal, or diffuse disease with reticular infiltrates.
  - Pleural effusions are present in ~20%.
  - Hilar adenopathy is seen in 7%–22%.
- *C trachomatis*
  - Chest radiograph typically demonstrates a lobar or interstitial pattern.
- *Aspergillus* species
  - Chest radiograph reveals wedge-shaped infiltrates and cavities.
  - CT
    - — May be helpful for early diagnosis of invasive aspergillosis.
    - — Halo sign (ground-glass attenuation surrounding a soft tissue nodule) is characteristic, and cavitation may follow.
- Blastomycosis
  - Chest radiograph shows infiltrates, reticulonodular pattern, and pleural effusion.
  - Cavitation is evident in some.
- Coccidioidomycosis
  - Chest radiograph tends to be nonspecific, with infiltrates, hilar adenopathy, and small pleural effusions.
  - Small percentage of patients have nodules or cavities early on, and 5%–10% have persistent pulmonary nodules or cavities.
    - — Cavities tend to be thin-walled and resolve spontaneously.
      - On occasion the cavities expand.
    - — If they are >6 cm, they are at risk for rupture, and surgery is indicated.
- Histoplasmosis
  - In some patients, a single pulmonary nodule is present in the lung parenchyma.
  - This nodule has the appearance of a coin lesion on chest radiograph.
- *L pneumophila*
  - Chest radiograph typically shows unilateral or bilateral bronchopneumonia.
- PCP
  - Typical radiographic appearance is diffuse bilateral infiltrates extending out from the hilum.
  - In the early stages the chest radiograph may be normal; later there may be pneumatoceles.
  - CT.
    - — Patchy areas of ground-glass appearance are suggestive, particularly in the patient with HIV.
- RSV
  - Radiographic appearance of lobar consolidation (especially right upper lobe) or a bronchopneumonia pattern
- Cytomegalovirus
  - Chest radiograph shows bilateral interstitial infiltrates.

DIAGNOSTIC PROCEDURES

- Bronchoalveolar lavage
  - May help define therapeutic choices
  - Useful for patients with
    - — Significant respiratory distress
    - — Clinical picture that fails to fall into a readily recognized category
  - May allow the discontinuation of certain antimicrobial drugs, alleviating risk of associated adverse reactions and cost
- Bronchoscopy with lavage
  - Particularly valuable in patients with immune defects
  - May be performed quickly with minimal morbidity in almost any child

- Should be considered early in the illness, before initiation of therapy with multiple antibiotics
  - — Increases yield of the test
- May not be available to every practitioner

TREATMENT APPROACH

- If clinical impression of pneumonia is high, bacterial etiology is likely, and antibiotics are indicated.
- The choice of antibiotic varies depending on age and organisms that are in the community.
  - In children 2 months–5 years: High-dose amoxicillin 80–90 mg/kg/d for 7 days is recommended.
- For hospitalized patients with uncomplicated pneumonia, ampicillin, penicillin, or, alternatively, a third-generation cephalosporin is preferred.
- Resistant strains.
  - 17%–35% of *S pneumoniae* isolates from CAP in the United States are resistant to penicillin G.
  - 15% are resistant to macrolides, which may indicate an alternative when bacterial pneumonia is suspected.
    - — However, resistance to penicillin by *S pneumoniae* is a different mechanism from that of *S aureus* and in most otherwise healthy children can be overcome by higher doses of penicillin, ampicillin, or amoxicillin.
  - Although mycoplasma infection does occur in children <5 years, a macrolide may not be the best antibiotic choice for empiric treatment at this age, in part because many *S pneumoniae* are now resistant to macrolides or azides.
- If the child is vomiting or otherwise unable to take oral medications, the recommendation is a single initial dose of ceftriaxone prior to attempting oral antibiotics.
- Recommendation for children ≥5 years is that a macrolide be added to treat CAP in the outpatient setting.
  - 7–14 days of erythromycin *or*
  - 5 days of azithromycin
- Alternatives include
  - Doxycycline for children >7 years
  - Levofloxacin alone for older adolescents
- Physicians should follow up with children who are diagnosed with pneumonia within 1–3 days.

SPECIFIC TREATMENTS

Bacterial Pneumonias

- Pneumococcal pneumonia
  - Clinical course is usually rapid, with response to antibiotics causing reduction of fever within a few hours.
  - In children with CAP, proven or suspected to be of bacterial origin, who are treated as outpatients, amoxicillin or amoxicillin-clavulanate is recommended.
  - In school-aged children (>5 years), the addition of a macrolide for coverage of atypical organisms is advised.
  - In children ill enough to warrant hospitalization, the use of penicillin, ampicillin, or ceftriaxone and the addition of a macrolide are usually appropriate.
  - Decisions for therapy should take into account local resistance patterns and immunization history.
- Group A streptococcus
  - Response to antibiotics tends to be slow, even with sensitive organisms.
  - Penicillin remains the treatment of choice, although ampicillin is an alternative.
- Staphylococcal pneumonia
  - If staphylococcal pneumonia is suspected, the increased prevalence of MRSA requires vancomycin or clindamycin for initial treatment until sensitivities are known.
  - Physicians should be aware of their local MRSA susceptibilities for these agents.
- *Pseudomonas* pneumonia
  - Treatment should be with 2 antibiotics, usually an aminoglycoside and a β-lactam antibiotic.
  - Children with chronic *Pseudomonas* infection, especially those with CF, may have a major problem with resistance to antibiotics.
- *Klebsiella pneumoniae*
  - Hospitalization is indicated, including for CAP, because even with treatment there is significant mortality.
  - Many *Klebsiella* organisms are resistant to multiple antibiotics, so, rather than monotherapy, multiple antibiotics are indicated until antibiotic sensitivities are available.
    - — Potential choices include third-generation cephalosporins (eg, cefotaxime, ceftriaxone), carbapenems (eg, meropenem), aminoglycosides, and quinolones.

- Extended-spectrum β-lactamase and carbapenemase-resistant strains may occur; thus, pediatricians should consult with an infectious disease specialist.

- *L pneumophila*
  - Azithromycin is the drug of choice for suspected or confirmed *Legionella* pneumonia.
    - Begin administration intravenously, converting to orally when the child responds.
  - Fluoroquinolones are bactericidal and can be used in adolescents and adults as well as immunocompromised patients.
- Mycoplasma
  - Macrolide antibiotics are recommended, although there are now reports of macrolide resistance.
  - Tetracycline is active, in particular doxycycline, and can be used for adolescents, but not for children <8 years.
  - Alternatives include the newer fluoroquinolones.
  - β-lactams are not effective, nor is trimethoprim.
  - Most cases of CAP improve in a matter of days with no residual findings.
- *C trachomatis*
  - For infants, azithromycin 10 mg/kg every 24 hours for 5 days.
  - Erythromycin ethylsuccinate, 50 mg/kg/d divided into 4 doses for 14 days, is an alternative.
- *C pneumoniae*
  - Azithromycin is effective.
  - Doxycycline can be used in older children and adolescents.

Viral Pneumonias

- Influenza virus
  - Symptoms last for several days and are treated with over-the-counter medications.
  - Aspirin is not recommended because of its association with Reye syndrome.
  - Oseltamivir (Tamiflu) is approved for oral administration in persons >1 year with influenza A or B who have been symptomatic for ≤2 days.
    - Can be given to infants <1 year with reduced dosage.
  - Although vaccination is the preferred approach for prevention, zanamivir and oseltamivir, with specific age considerations, are recommended for prophylaxis of influenza infection.
- Cytomegalovirus
  - Ganciclovir is used as prophylaxis in transplant patients at risk (eg, a seropositive donor and seronegative recipient).
    - It is also beneficial for symptomatic patients with pneumonia.
- Varicella
  - Treated with acyclovir.
  - Children with varicella pneumonia should be hospitalized.
- Herpes simplex virus
  - Acyclovir 5 mg/kg every 8 hours intravenously or 400 mg orally 5 times per day

Fungal Pneumonias

- *Aspergillus*
  - Voriconazole has become the treatment of choice for invasive aspergillosis.
  - Rapid institution of treatment is necessary because invasive aspergillosis can be rapidly progressive.
  - Posaconazole or amphotericin B may be considered if there is a possibility of mucor.
  - Caspofungin has been approved for treatment of invasive aspergillosis if there is resistance or intolerance to other therapies.
  - Consultation with an infectious disease specialist is indicated.
- *Candida* species
  - Fluconazole is the treatment of choice for the non-neutropenic patient.
    - Intravenous (IV) at first; with improvement, can be switched to oral
  - Voriconazole may be a better alternative if other molds may be involved.
  - Echinocandins (eg, caspofungin) may be a better selection with more severe infections and in high-risk patients.
    - Especially if the infection is non-albicans, such as *Candida glabrata* and *Candida krusei*
- Blastomycosis
  - Amphotericin B for moderate to severe disease, until improvement is noted
    - Patient then can switch to itraconazole for 6–12 months.
  - For mild to moderate disease, itraconazole for 6–12 months
- Coccidioidomycosis
  - Most immunocompetent patients do not require treatment, but the following signs and symptoms are considerations for treatment:
    - Continuous fever for >1 month
    - Night sweats for >3 weeks

  - Weight loss >10%
  - Large (>50% of 1 lung) or bilateral pulmonary infiltrates
  - Primary infection during infancy
  - Primary infection during pregnancy, especially in the third trimester or immediately postpartum
  - Immunosuppression
  - Diabetes mellitus or preexisting cardiopulmonary disease
- Treatment of acute pulmonary coccidioidomycosis includes oral azoles, such as fluconazole.
- During pregnancy amphotericin B is preferred because the azoles may be teratogenic.
- Uncommon in children.
  - Those with disseminated disease or progressive fibrocavitary disease may require prolonged treatment up to 1 year.

■ Histoplasmosis
- Acute pulmonary histoplasmosis that is asymptomatic or mild requires no treatment.
- If symptoms are prolonged for >4 weeks, oral itraconazole for 6–12 weeks.
- If there is severe infection, treatment should be initiated with amphotericin B for 1–2 weeks, followed by a year of itraconazole.

■ PCP
- Treatment depends on the degree of hypoxemia.
- Trimethoprim-sulfamethoxazole (TS) is the treatment of choice.
  - Given orally for mild cases, although most patients require IV treatment, at least at first.
- IV pentamidine is an alternative, especially if there is a reaction to TS.
- Duration of treatment is
  - 21 days for patients with HIV.
  - 14 days for patients without HIV.
  - Similar durations should be given based on severity of disease (mild vs severe).
- Corticosteroids may be useful in severe disease.
- Chemoprophylaxis against PCP is indicated for patients with HIV and those who are immunocompromised, especially transplant patients and those with primary and acquired immunodeficiency.
  - The standard regimen is oral TS, 3 consecutive days per week.
  - If this is not tolerated, nebulized pentamidine is an alternative.
- Infectious disease and pulmonary consultation are recommended.

WHEN TO ADMIT

■ Hospitalization is indicated with
- Oxygen saturation consistently <90% (definite).
- Suspected sepsis (definite).
- Severe dehydration (definite).
- Inability to drink fluids (possible).
- Moderate or severe respiratory distress (possible).
- Failed outpatient antibiotic treatment (clinical judgment).
- Home circumstance or social situation raises concerns (likely).
- Infants <6 months (unless ideal caregiver).

■ RSV.
- Infants <2 months and those with significant respiratory distress or apnea

■ Varicella pneumonia.

■ Children with pneumonia and a chronic illness (eg, if they are immunocompromised).

■ Currently, validated screening systems do not exist to help predict which children with pneumonia should be hospitalized.

WHEN TO REFER

■ Children with complications (eg, pleural effusion, prolonged hypoxia) should be referred to a pulmonologist.

■ If the child has a chronic illness, consultation with the specialist who is involved in his or her long-term care may be helpful.

■ Consultation with infectious disease or allergy specialists is indicated when allergies, comorbid conditions, or unresponsiveness to antibiotics are present.

COMPLICATIONS

■ Combined effects of malnutrition and inadequate immunization may cause much more severe respiratory disease for children.
- Particularly for those without access to advanced therapy to treat underlying infection and subsequent complications

■ Pneumococcal pneumonia.
- Complications may be systemic, with meningitis, carditis, peritonitis, and septic arthritis resulting from bacteremia.
- Pulmonary complications include pleural effusion and empyema.
- Inappropriate secretion of antidiuretic hormone is common and may cause significant reduction of serum sodium.

- Group A streptococcus
  - Complications are common and include pneumothorax, pneumatoceles, bronchiectasis, and bronchopleural fistula.
- *Pseudomonas*
  - Untreated *Pseudomonas* pneumonia may progress rapidly to necrotizing bronchopneumonia.

PROGNOSIS

- Bacterial
  - Most children with bacterial pneumonia improve without sequelae.
  - Bacterial pneumonia is an important cause of death if untreated, especially in developing countries.
  - Children with preexisting conditions may be at increased risk for morbidity, including subsequent infections because of scarring in the lungs.
  - The immune status of the child affects the risk of mortality and morbidity.
  - *C pneumoniae.*
    - Mortality of 9.8% has been reported in patients with sickle cell disease.

PREVENTION

- 13-valent pneumococcal conjugate vaccine (PCV-13), approved in February 2010, is recommended for all children from 2 months–5 years of age.
- The Centers for Disease Control and Prevention (CDC) recommends that all individuals ≥6 months get a seasonal flu vaccine.
  - May be given to children as young as 6 weeks
- Seasonal flu vaccine protects against 3 or 4 influenza viruses and varies in composition according to research indicating likely common strains during the upcoming season.
- Children on chronic aspirin therapy should not receive the vaccine because of the risk of Reye syndrome.
- The CDC recommends that people in contact with certain groups of children get a seasonal flu vaccine to better protect the child (or children) in their lives from the flu.
  - Close contacts of children <5 years (people who live with them), especially infants <6 months
  - Out-of-home caregivers (eg, nannies, child care providers) of children <5 years
  - People who live with or have other close contact with a child or children of any age with a chronic health problem (eg, asthma, diabetes)
  - All health care workers, to keep from spreading the flu to their patients
- Additional considerations are *Haemophilus influenzae* type b vaccine and varicella vaccine.
- Surveillance is indicated for serotypes not included in the vaccine.
  - Although invasive pneumococcal disease has decreased, complicated pneumonia has increased significantly across the United States, and these cases tend to be from non-vaccine serotypes.
- PCV-13 coupled with pneumococcal polysaccharide vaccine (PPSV-23) is now recommended for children and adults with certain chronic medical conditions or cochlear implants to provide greater protection.

Polyuria

DEFINITION

- Clinical definition: urine production >2 L/m^2 per 24 hours
- Functional definition: inappropriately high urine output relative to circulating volume and osmolarity

HISTORY

- A detailed history often reveals the cause of polyuria.
  - Age at onset
  - Pattern of fluid intake
  - Rate of onset
  - Feeding history
    - To identify infants who have water intoxication
- Urine output >5 mL/kg/h in a child should raise concerns.
- Polyuria often is associated with
  - Polydipsia
  - Frequent urination
  - Nocturia
    - New onset of nocturia often is the first manifestation of loss of concentrating ability.
- Differentiating polyuria from other conditions depends on total urine output.
  - If the exact daily urinary volume is unknown, a detailed history of fluid intake and urinary habits is helpful.
- With an older child, parents may notice increased fluid intake rather than polyuria.

PHYSICAL EXAMINATION

- Infants with polyuria do not have independent access to fluids and may fall into negative water balance, resulting in
  - Weight loss
  - Dehydration
  - Electrolyte disturbances

DIFFERENTIAL DIAGNOSIS

Systems Involved in Maintenance of Serum Osmolality and Water Balance

- In reaching a diagnosis in a patient who has polyuria, the clinician must consider systems involved in maintaining normal serum osmolality and water balance.

Neurogenic Vasopressin Deficiency

- Congenital
  - Familial
  - Brain malformations
    - Septo-optic dysplasia
    - Holoprosencephaly
    - Encephalocele
- Acquired
  - Head trauma
  - Vascular event
    - Thrombosis
    - Hemorrhage
  - Postinfection
    - Meningitis
    - Encephalitis
    - Congenital cytomegalovirus
    - Toxoplasmosis
  - Tumor
    - Craniopharyngioma
    - Germinoma
    - Optic glioma
  - Systemic infiltrative diseases
    - Histiocytosis
    - Syphilis
    - Tuberculosis
    - Sarcoidosis
  - Inflammatory
    - Lymphocytic hypophysitis
  - Guillain-Barré syndrome
  - Autoimmune disorders
- Idiopathic

Renal Vasopressin Insensitivity

- Familial nephrogenic diabetes insipidus
  - V2-receptor gene defect (X-linked)
  - Aquaporin 2 gene defect (autosomal recessive)
- Acquired
  - Post-obstructive
  - Drug-induced
    - Lithium
    - Amphotericin B
  - Associated with systemic disease
    - Sickle cell disease
    - Sarcoidosis
    - Amyloidosis
  - Metabolic
    - Hypercalcemia
    - Hypokalemia

Other Renal Disorders

- Renal tubular defects
  - Cystinosis
  - Distal renal tubular acidosis
  - Bartter syndrome
  - Renal Fanconi syndrome
  - Arthrogryposis-renal tubular dysfunction-cholestasis (ARC) syndrome
- Nephronophthisis

Excessive Fluid Intake

- Primary polydipsia
- Water intoxication

Osmotic Diuresis

- Diet induced
- Drug induced
- Diabetes mellitus (type 1 or 2)

Diabetes Insipidus

- Characterized by
  - Polyuria
  - Polydipsia
  - Dilute urine
  - Dehydration
  - Hypernatremia
  - Growth failure
- Hypernatremia and dehydration may cause irritability in young children.

Central Diabetes Insipidus

- When a diagnosis of central diabetes insipidus has been made, studies must be undertaken to ascertain the cause.
  - Although many cases are idiopathic, thorough evaluation for an underlying lesion must be conducted.
  - Once vasopressin deficiency has been identified, full investigation of other pituitary functions, visual field examination, and magnetic resonance imaging (MRI) of the brain will likely be the next steps in evaluation.
- In familial neurohypophyseal diabetes insipidus symptoms typically do not occur until 5–10 years of age.
- Wolfram (DIDMOAD) syndrome typically presents in early childhood.
  - **D**iabetes **i**nsipidus, **d**iabetes **m**ellitus, **o**ptic **a**trophy, and **d**eafness
- After head trauma or surgery, patients may have a period of antidiuresis after transient polyuria, followed by persistent central diabetes insipidus (triple-phase response).
- In recent years, fewer cases of diabetes insipidus have been diagnosed as idiopathic; more have been diagnosed as secondary to central nervous system (CNS) infection or intracranial birth defects.
  - Autoantibodies to hypothalamic vasopressin cells have been detected in some children previously thought to have idiopathic diabetes insipidus.
  - About 50% of the patients who have histiocytosis also have vasopressin cell autoantibodies.
- In adolescents with acquired lymphocytic or granulomatous, hypophysitis, hyperprolactinemia, and other anterior pituitary dysfunction may accompany diabetes insipidus.
- The underlying lesion may not be evident at the initial evaluation.

Nephrogenic Diabetes Insipidus

- Inherited forms of nephrogenic diabetes insipidus are rare.
  - Symptoms of profound polyuria typically occur within the first weeks of life.
    - Vomiting
    - Fever
    - Failure to thrive
    - Hypernatremic dehydration
      - Recurrent hypernatremic dehydration may lead to CNS damage or even death.
      - Breastfed infants may show signs later than those who are bottle-fed because of the lower osmotic load in human milk.
  - Older children and adults may be able to adjust oral fluid intake to maintain serum osmolality.
  - A rare form of autosomal-recessive nephrogenic diabetes insipidus has been described in patients with mutations in the gene for the water-channel protein aquaporin 2.
  - Other renal tubular defects in which vasopressin resistance has been observed must be considered.
  - An association between nephrogenic diabetes insipidus and the ARC syndrome has been recognized.
    - Affected children are prone to severe growth impairment, intellectual disability, and deafness.
- The risk factors for acquired, often reversible vasopressin insensitivity, include
  - Lithium.
    - Longer duration of treatment with lithium correlated with increased risk of irreversible diabetes insipidus
  - Antibiotics.
  - Antifungals.
  - Antineoplastic agents.
  - Antivirals.
  - Metabolic disturbances can result in reversible vasopressin resistance.
  - Hypercalcemia and hypokalemia each may be associated with nephropathy in which tubular ability to conserve water is lost.

- Certain systemic disorders may cause renal tubular dysfunction and result in polyuria.
  - — Sickle cell disease
  - — Sarcoidosis
  - — Amyloidosis

Excess Water Intake

- Polyuria may be a consequence rather than a cause of excessive fluid intake.
- Primary polydipsia, or compulsive water drinking, is a rare cause in childhood.
  - Most common in older children or adults who have emotional disturbances.
  - About 80% of cases are believed to occur in girls and women.
  - Onset is gradual.
  - Some investigators believe the disorder to be caused by a primary psychiatric disturbance, associated with schizophrenia and termed *psychogenic polydipsia*.
  - One study in adults showed evidence of a defect in water excretion, osmoregulation of water intake, and vasopressin secretion.
- Typical antipsychotic drugs (eg, haloperidol) have been associated with worsening of polydipsia.

Osmotic Diuresis

- May cause polyuria with renal water loss.
- Glycosuria often is found to be the cause of sudden onset of polyuria in children with uncontrolled diabetes mellitus.
  - In type 1 and type 2 diabetes mellitus, diminished carbohydrate use results in hyperglycemia and glycosuria.
  - When present in urine at high concentrations, glucose acts as an osmotic diuretic, resulting in polyuria.
- Chronic hyperglycemia can cause a form of partial nephrogenic diabetes insipidus.
- Treatment with large volumes of dextrose-containing intravenous (IV) fluids can result in hyperglycemia and polyuria.
- In contrast, renal glycosuria is characterized by a defect in renal tubular reabsorption of glucose, resulting in glycosuria without hyperglycemia or polyuria.
- Osmotic diuresis also may be provoked by
  - Mannitol
  - Radiologic contrast agents
  - High-protein feedings (in which urea acts as the osmotic agent)
  - Release of bilateral urinary tract obstruction

LABORATORY EVALUATION

- Baseline values
  - Serum sodium level (mEq/L)
    - — Reference range: 135–145
    - — Central diabetes insipidus: normal or elevated
    - — Nephrogenic diabetes insipidus: normal or elevated
    - — Psychogenic polydipsia: low normal
  - Serum osmolality (mOsm/kg)
    - — Reference range: 285–290
    - — Central diabetes insipidus: normal or elevated
    - — Nephrogenic diabetes insipidus: normal or elevated
    - — Psychogenic polydipsia: <280
  - Urine osmolality (mOsm/kg)
    - — Reference range: 50–1,200
    - — Central diabetes insipidus: <200
    - — Nephrogenic diabetes insipidus: <300
    - — Psychogenic polydipsia: <200
  - Plasma vasopressin
    - — Central diabetes insipidus: low
    - — Nephrogenic diabetes insipidus: normal or elevated
    - — Psychogenic polydipsia: low
- Urine osmolality is best interpreted with a concomitant serum sample.
  - A hyperosmolar state suggests vasopressin deficiency or insensitivity, provided that the serum glucose concentration is normal.
  - Low serum osmolality with hyponatremia suggests primary polydipsia or water intoxication.
  - Serum sodium usually is normal in diabetes insipidus as long as free access to fluids exists and thirst mechanism is intact.
  - Hypernatremia is commonly seen in infants with diabetes insipidus or when a central lesion exists that also impairs thirst.
- Blood chemistries with urea nitrogen and creatinine will detect causes of nephrogenic diabetes insipidus, such as hypercalcemia and renal impairment.
- 24-hour measurement of fluid intake and output.
  - Useful for confirming polyuria before ordering laboratory tests
- Urinary specific gravity on a first-voided morning specimen can be affected by the presence of glycosuria, proteinuria, or radiocontrast material.
  - Both types of diabetes insipidus and primary polydipsia result in relatively dilute urine.

- Disorders resulting in renal tubular damage, such as sickle cell disease, are more likely to have isosthenuria with specific gravities of ~1.010.

- Urinalysis with microscopy performed on a first-voided morning specimen also provides valuable information.
  - Protein, casts, or formed blood elements in the urine suggest a renal disorder.
  - Glycosuria with ketonuria strongly suggests diabetes mellitus.
- Complete blood cell count and liver function tests may be part of the basic workup.

IMAGING

- When central diabetes insipidus has been diagnosed, studies must be undertaken to ascertain the cause.
  - MRI of the pituitary and hypothalamus to assess for
    - Pituitary masses
    - Craniopharyngioma
    - Pinealoma
    - Pituitary stalk abnormalities

DIAGNOSTIC PROCEDURES

Water Deprivation Test

- In children with low urine specific gravity, polyuria, and no glycosuria, the next step in evaluation is referral to a specialist for a formal water deprivation test to determine if a defect exists in vasopressin production or renal responsiveness.
- Should be undertaken with great caution in younger children.
- Should not be performed in newborns.
- Should follow a 24-hour period of free access to fluids.
- Because of the possibility of volume depletion, the study should be carried out during the day, when supervision is optimum.
- At baseline, the clinician should
  - Record vital signs and weight.
  - Obtain blood and urine for
    - Osmolality
    - Urine specific gravity
    - Serum sodium concentration
    - Serum urea nitrogen level
    - Hematocrit
- Blood also should be obtained at the beginning and conclusion of fluid deprivation to determine plasma vasopressin (antidiuretic hormone [ADH]) levels.
  - These may be helpful if the response to the water deprivation test is equivocal.
- Fluid intake is restricted for up to 8 hours, during which the patient must be supervised closely to avoid surreptitious drinking.
  - In patients with very low urine osmolality who are strongly suspected of having nephrogenic diabetes insipidus, the response to exogenous ADH can be determined without the need for prior fluid deprivation.
- The patient should be weighed and have vital signs recorded every 2 hours for the first 4 hours, then hourly.
- Blood and urine should be collected after 4 hours, then every 2 hours, for measurement of
  - Osmolality
  - Serum sodium
  - Urine specific gravity
- The test should be terminated when one of the following end points is reached:
  - The patient has lost ≥5% of body weight.
  - Urine specific gravity is >1.020.
  - Urine osmolality exceeds 600 mOsm/kg.
  - Plasma osmolality exceeds 300 mOsm/kg.
  - Serum sodium exceeds 147 mEq/L.
- At the conclusion of the test
  - Weight and vital signs are recorded.
  - Blood and urine are collected for measurement of
    - Osmolality
    - Serum sodium
    - Urine specific gravity
- In healthy children, and in most children with primary polydipsia
  - Weight remains constant.
  - Urine specific gravity increases.
  - Urine volume decreases.
- Concentrating ability
  - Often impaired in primary polydipsia
  - Maximal urine osmolality of 500–600 mOsm/kg, compared with >800 mOsm/kg in healthy individuals
- Diabetes insipidus should be suspected in the setting of
  - Continued diuresis
  - Dehydration
  - Weight loss
  - Hyperosmolarity

- A small increase in urine osmolality may occur in both forms of diabetes insipidus from partial vasopressin deficiency (central) or partial vasopressin resistance (nephrogenic).
- Administration of exogenous vasopressin (ADH) may help differentiate between the 2 disorders.
  - In an older child, the test can be performed after water deprivation test or at a subsequent visit.
  - Extreme caution is required with infants or small children because of the danger of fluid overload and hyponatremia.
  - Patient is given free access to water after administration of desmopressin acetate, a synthetic derivative of vasopressin.
  - Intake, output, and urine specific gravity are recorded every 30–60 minutes.

Interpretation of Water Deprivation Test

- Clinical situation: typical
  - Plasma vasopressin: increased
  - Urine osmolality: >800
  - Urine specific gravity after vasopressin: increased
- Clinical situation: central diabetes insipidus
  - Plasma vasopressin: low
  - Urine osmolality: <300
  - Urine specific gravity after vasopressin: increased
- Clinical situation: nephrogenic diabetes insipidus
  - Plasma vasopressin: high
  - Urine osmolality: <200
  - Urine specific gravity after vasopressin: unchanged
- Clinical situation: psychogenic polydipsia
  - Plasma vasopressin: unchanged
  - Urine osmolality: 500–600
  - Urine specific gravity after vasopressin: unchanged/increased

TREATMENT APPROACH

- Management of polyuria depends largely on the underlying diagnosis and must be individualized.
- Patients often are found to have a chronic disease that requires close, long-term surveillance.

SPECIFIC TREATMENT

Central Diabetes Insipidus

- In a severely ill patient, aqueous vasopressin, 0.1–0.2 units/kg, subcutaneously every 4–6 hours
  - Vasopressin may also be given by continuous IV infusion.
  - Reported starting doses vary from 0.5–4.6 mU/h; doses should be increased or decreased as needed.
- Once the child's condition has stabilized, management consists of desmopressin acetate.
  - Desmopressin can be administered orally in tablet form or instilled intranasally.
  - Should be given at the lowest dose that produces antidiuretic effect.
  - Intranasally.
    - Total daily dose may range from 5 mcg in infants to 40 mcg in older children, divided into 2 or 3 doses as needed.
    - Children receiving dose multiples of 10 mcg may use nasal spray; those on smaller or intermediate doses must use a rhinal tube.
  - Orally.
    - Therapeutic doses of oral desmopressin generally are 15–20× larger than intranasal doses.
    - Greater variability exists in the effective dose.
    - Response to treatment must be monitored closely if the route of administration is changed.
- Treatment of small children and infants with central diabetes insipidus can be difficult, with rapid changes in serum osmolality potentially leading to complications.
- Parents must carefully monitor fluid intake and output in younger children.
- Because young infants are fed liquids exclusively and have high fluid requirements, vasopressin can greatly increase risk of severe hyponatremia.
  - These children are best managed with fluid therapy alone.
  - Small doses of desmopressin may be required
    - If adequate fluid intake is difficult to maintain
    - If caloric intake is inadequate because of excessive fluid consumption
  - The risk of hyponatremia can be reduced by allowing escape from the antidiuretic effect for 1 hour before the next dose.
- A child with adipsia or hypodipsia is best managed by fixing the desmopressin dose and fluid intake.
- Daily weights and frequent sodium levels are useful in assessing fluid status at home.

Nephrogenic Diabetes Insipidus

- Children with nephrogenic diabetes insipidus should be allowed free access to fluids.
- Parents of infants who have this disorder need to offer frequent water feedings to allow infants to maintain osmotic homeostasis.
- A low-salt diet has been helpful in reducing urine output.

- Thiazide diuretics can reduce polyuria further by reducing amount of urine delivered to the distal tubule.
  - Indomethacin and amiloride, when given concurrently with a thiazide, have been found effective at reducing urine output.

Primary Polydipsia

- Once a neurogenic lesion or gene mutation has been ruled out, medical therapy is not indicated.
- Psychiatric evaluation may be useful in addressing the origin of the polydipsia.
- Clozapine has been reported to reduce excessive water intake.

Osmotic Diuresis

- Osmotic diuresis induced by drugs or diet generally is self-limited.
- In diabetes mellitus, polyuria secondary to hyperglycemia and glycosuria resolves with treatment of the underlying condition.

WHEN TO REFER

- Hypotonic polyuria (confirmed by 24-hour urine and urine osmolality <300 mOsm)
- Need to perform water deprivation test
- Polyuria after neurosurgery
- Polyuria and polydipsia secondary to diabetes mellitus
- Structural renal diseases leading to polyuria should be referred to a pediatric nephrologist.
- Children with vasopressin deficiency are best referred to an endocrinologist or neurologist so that the cause of the diabetes insipidus can be determined.

WHEN TO ADMIT

- Polyuria and dehydration
- Diabetic ketoacidosis
- Severe hypernatremia
- Suspected diabetes insipidus in an infant
- Hypernatremia with MRI or neurologic findings suggestive of brain tumor

FOLLOW-UP

- Patients with diabetes insipidus should be closely observed, after diagnosis, until an appropriate dose of desmopressin acetate is determined.

COMPLICATIONS

- Hypernatremia in patients with diabetes insipidus
- Hyponatremia in patients with psychogenic polydipsia
- Central pontine myelinosis if hyponatremia is corrected rapidly

Prader-Willi Syndrome

DEFINITION

- Prader-Willi syndrome (PWS) is a complex genetic syndrome characterized by
  - Extreme hypotonia and failure to thrive during infancy
  - Childhood-onset hyperphagia and obesity
  - Unique behavioral characteristics
  - Cognitive impairment
- Many manifestations of PWS seem to be related to insufficient functioning of the hypothalamus; however, the nature of the deficiency has not yet been identified.

SIGNS AND SYMPTOMS

Physical Characteristics

- Characteristic facial features are initially subtle and may be difficult to appreciate during infancy but become more evident as the child grows.
- Common physical findings include
  - Almond-shaped eyes
  - Small-appearing mouth with thin upper lip
  - Down-turned corners of the mouth
  - Narrow bifrontal diameter
  - Small and narrow hands and small feet
  - Hypopigmentation (fair skin, eyes, hair) in about one-third of individuals
  - Genital hypoplasia
  - Centrally distributed obesity
  - Short stature

Hypotonia and Feeding Difficulties

- Severe central hypotonia is the most common presenting symptom.
  - Has led to the recommendation that all infants with persistent hypotonia be tested for PWS
- Prenatal in onset, resulting in
  - Decreased fetal movements
  - Abnormal fetal position
  - Increased occurrence of cesarean delivery
- Infant may seem floppy, have a weak cry, and exhibit decreased arousal.
- Feeding problems often lead to failure to thrive.
  - Poor suck
  - Lack of awakening to feed
- Hypotonia gradually improves with age, but most adults remain mildly hypotonic with decreased muscle bulk and tone.

Obesity

- Between 1 and 6 years of age, children demonstrate hyperphagia and have an insatiable appetite.
  - Obsessive behavior surrounding food
  - Food-seeking behavior, hoarding, stealing, and eating undesired food, such as garbage, frozen food, or spoiled food
- Decreased need for caloric intake because of low metabolic rate and less mean muscle mass.

Hypogonadism

- Hypogonadism with genital hypoplasia during infancy; may become more apparent as the child grows.
- In males
  - Scrotal hypoplasia
  - Cryptorchidism
  - Small penis or testes for age
- In females
  - Present but difficult to assess
- Becomes more apparent in adolescence because of abnormal and incomplete pubertal development.
  - Precocious puberty is uncommon, but precocious adrenarche has been reported.
  - Females usually exhibit oligomenorrhea or amenorrhea.
  - Males have scant body hair and poor voice change.
  - Adolescents lack the pubertal growth spurt, resulting in short stature.
    - Deficiency of growth hormone and insulin-like growth factor 1 contribute to short stature.

Sleep Disturbance

- Sleep-disordered breathing is common.
- Excessive daytime sleepiness, abnormal circadian rhythm in rapid eye movement sleep, abnormal arousal, and central sleep apnea have all been reported.
- Obesity contributes to obstructive sleep apnea, but sleep is abnormal even in its absence.

Musculoskeletal Problems

- Hip dysplasia in ~10%.
- Scoliosis is common and can develop at any time during childhood.
- Kyphosis occurs frequently, usually developing in adolescence or early adulthood.
- Osteoporosis is common in adults and may be the result of hypotonia, low calcium intake, hypogonadism, and growth hormone deficiency.

Developmental Delay or Intellectual Disability

- Early developmental milestones are delayed.
  - Average age of sitting is 12 months and of walking is 24 months.
- Language milestones are delayed.
  - First words from 18 months–6 years.
  - Articulation difficulties are common.

- Intelligence testing has revealed a range from low-normal to severely impaired.
  - Most individuals function in the range of mild intellectual disability.
  - Relative strengths include visual-spatial skills, reading, expressive vocabulary, and long-term memory (eg, exceptional skills with jigsaw puzzles).
  - Weaknesses are seen in sequential processing and short-term memory.

Behavior

- Unique behavioral characteristics, including
  - Temper tantrums
  - Stubbornness
  - Obsessive-compulsive behaviors
  - Inflexibility
- Often begin around the age of 3–4 years and often are related to cravings for food.
  - Individuals may be manipulative, lie, steal, and become aggressive in their quest for food.
- ~25% of individuals with PWS have been diagnosed with autism spectrum disorder (higher rate in individuals with maternal uniparental disomy [UPD]).
- ~5%–10% of individuals develop psychosis in early adulthood.

Additional Findings

- Ophthalmologic findings, including strabismus, refractive errors, and hyperopia, are often present.
- Decreased saliva volume is common and leads to dry mouth and possible increase in dental caries.
  - Thick and viscous saliva may contribute to articulation difficulties.
- Other findings possibly related to abnormalities in hypothalamic functioning include
  - Altered temperature perception
  - High pain threshold
  - High vomiting threshold

DIFFERENTIAL DIAGNOSIS

- Differential diagnosis can vary depending on the age.
- In infancy includes other disorders that present with hypotonia, feeding difficulties, or failure to thrive.
  - Spinal muscular atrophy
  - Congenital myotonic dystrophy type 1
  - Angelman syndrome
  - Botulism
  - Additional neuromuscular or genetic disorders
- In childhood includes conditions that present with intellectual disability and obesity.
  - Fragile X syndrome
  - Bardet-Biedl syndrome
  - Alstrom syndrome
  - Cohen syndrome
  - Börjeson-Forssman-Lehmann syndrome
  - Albright hereditary osteodystrophy

DIAGNOSTIC APPROACH

- If PWS is suspected based on the clinical criteria, confirm by genetic testing.
  - Order of testing may vary, depending on previous studies and availability of tests.
  - Referral to a clinical geneticist may be appropriate and may allow more targeted testing.
- DNA methylation is usually the first step.
  - Detects 99% of PWS cases.
  - If biparental inheritance is identified, PWS is ruled out; if only maternal alleles are detected, PWS is confirmed.
- For genetic counseling purposes, testing should continue until the specific cause is known.
  - After confirmation by methylation studies, fluorescence in situ hybridization, UPD studies, and sequence analysis can determine the specific cause (deletion, UPD, or imprinting error).

LABORATORY FINDINGS

- Because strict clinical criteria are not necessary for diagnosis, suggested criteria have been developed to prompt DNA testing (**Table 1**).

TREATMENT APPROACH

- A multidisciplinary approach should be used.
  - Treatment team often includes medical physicians, psychologists, dietitians, nurses, and therapists, with the primary care pediatrician overseeing and coordinating care.
  - Subspecialists in genetics, endocrinology, development and behavior, and pulmonology should be part of the care team.
  - Genetic counseling and referral to parental support groups should occur at diagnosis.

SPECIFIC TREATMENTS

Hypotonia and Feeding

- Adequate nutrition and growth are the major focus in infancy.
  - Gavage feeding or use of a special nipple to compensate for hypotonia and poor suck.

Table 1. Criteria to Prompt DNA Testing for Prader-Willi Syndrome

Age of Assessment	Features Sufficient to Prompt DNA Testing
Birth–2 y	Hypotonia with poor suck
2–6 y	Hypotonia with history of poor suck Global developmental delay
6–12 y	History of hypotonia with poor suck (Hypotonia often persists.) Global developmental delay Excessive eating (hyperphagia; obsession with food), with central obesity if uncontrolled
13 y–adulthood	Cognitive impairment; usually mild intellectual disability Excessive eating (hyperphagia; obsession with food), with central obesity if uncontrolled Hypothalamic hypogonadism or typical behavior problems (including temper tantrums and obsessive-compulsive features)

From Gunay-Aygun M, Schwartz S, Heeger S, O'Riordan MA, Cassidy SB. The changing purpose of Prader-Willi syndrome clinical diagnostic criteria and proposed revised criteria. *Pediatrics.* 2001;108(5):e92.

- Feeding schedule should be created, and the infant should be awakened to be fed.
- Fats are necessary for the development of the nervous system and should not be limited.
- Height and weight should be plotted monthly on a growth curve to monitor progress.
- Dietitian may be helpful in monitoring adequate caloric intake with a goal of keeping the infant between the 50th and 75th percentiles on the weight-for-length curve.

Obesity

- No medications have been successful in controlling the appetite of an individual with PWS.
- Weight should be managed with the combination of
  - Restrictive diet
    - Often started around preschool with frequent weight assessment to guide further recommendations.
    - Detailed food logs are useful for the family and allow professionals to calculate caloric intake.
    - Daily multivitamin and calcium and vitamin D supplements recommended to compensate for suboptimal intake of the restricted diet.
    - Use of positive reinforcement with a token economy may increase compliance.
  - Limited access to food
    - Access should be limited and locks placed on the refrigerator, cabinets, and garbage cans.
  - Exercise
    - 30–60 minutes of physical activity daily
  - Behavioral techniques
    - Healthy eating habits should be taught from an early age.
    - Consistent daily schedules for meals and exercise.

Hypogonadism

- Males should be evaluated for cryptorchidism with referral for surgical intervention when appropriate.
- Hormone replacement therapy may be considered in the pubertal years in consultation with an endocrinologist.
  - Estrogen replacement in females may be beneficial for bone density.

Growth Hormone

- Growth hormone replacement is approved for use in children, and stimulation testing is not required.
- The age for starting usually begins in early childhood but remains controversial.
  - Studies have shown benefits with starting at 6 months–1 year of age.
  - Early replacement has been shown to improve childhood growth, lean body mass, and adult height and may have an effect on overall development.

- Cases of sudden respiratory death have been reported.
  - These individuals had a history of significant obesity and preexisting respiratory or other contributing complications.
  - Deaths were not clearly related to growth hormone replacement, but care should be taken when initiating therapy.
  - A sleep study and respiratory evaluation are often recommended.
  - Obstructive sleep apnea should be treated before starting.
- Individuals should be screened before and during therapy for
  - Diabetes
  - Hypothyroidism
  - Scoliosis (with radiograph)

Development and Behavior

- Early intervention referral is recommended in infancy because of problems associated with hypotonia, motor delays, and language delays.
- With transition into school, an education plan should be developed.
  - Psychoeducational testing to assess individual strengths and weaknesses.
  - Continued therapy, classroom aides, behavior plans, and supervised lunches should all be discussed with the educational team.
- Children with PWS often respond well to structured environments and schedules.
  - Limits should be set and consistently enforced starting at an early age.
  - A specialist in development and behavior can help the family set limits and construct behavior plans to prevent more severe behavior problems in the future.
- Children with PWS often respond well to positive reinforcement and the use of a token economy.
- Skin picking can be quite difficult to treat, but behavioral strategies should be used, with reinforcement for alternative behaviors.
- For obsessive traits, tantrums, and food-seeking behaviors, children and their parents often benefit from behavior counseling.
- Psychopharmacologic agents may be considered.
- Individuals should be referred to a psychiatrist for signs of psychosis, such as hallucinations, behavior changes, or disorientation.

WHEN TO REFER

- Specialist referrals and timing are shown in **Table 2.**

FOLLOW-UP

- Individuals with PWS will require a supportive environment throughout their lives.
- Routine medical care.
  - Clinical screening for scoliosis and kyphosis at routine health care visits with radiographs as needed
  - Eye evaluation for strabismus (cover/uncover test), with a referral to ophthalmology if indicated
  - Regular dental visits and good dental hygiene
  - Examination of the skin because of picking behavior, possible infection, and bleeding
    - Keep nails short and clean.
    - Cover wounds.
- Monitor for known complications of obesity.
  - Regular blood pressure checks
    - Treat hypertension as in the general population.
  - Glycosylated hemoglobin and a lipid profile annually in obese adults
    - Treat type 2 diabetes as in the general population.
- Because of high pain threshold in PWS, all complaints of pain or change in behavior or appetite should be taken seriously.

COMPLICATIONS

- Obesity is the major cause of morbidity and mortality in PWS, often leading to secondary conditions.
  - Cardiopulmonary compromise.
  - Sleep apnea.
  - Type 2 diabetes mellitus.
  - Hypertension.
  - Overeating has resulted in gastric necrosis and rupture.
- Musculoskeletal.
  - Hip dysplasia
  - Scoliosis
  - Kyphosis
- Central adrenal insufficiency.

PROGNOSIS

- PWS remains a complex condition, but regular follow-up with multidisciplinary health care professionals can lead to early intervention or prevention of common complications.

Table 2. Specialists in Management of Children With Prader-Willi Syndrome

Sign or Symptom	Appropriate Referrals
At diagnosis	Genetics Endocrine Early intervention programming, school programming
Feeding/gastrointestinal	
Poor feeding/suck (infancy)	Dietitian, speech therapist (feeding support)
Food seeking, hyperphagia (early childhood and beyond)	Specialized behavioral therapy for food seeking
Abdominal pain, vomiting, anorexia	Urgent medical workup, especially for gastric necrosis
Endocrine	
Weight gain	Pediatric endocrinology
Growth hormone deficiency	Surgical referral for cryptorchidism
Glucose intolerance	
Delayed puberty	
Hypogonadism	
Vision	
Strabismus (monitor eye alignment)	Ophthalmologist knowledgeable in pediatric conditions
Failed vision screen	
Dental	
At higher risk for caries because of decreased saliva production	Referral to dentist accustomed to working with children with delays Reinforce good dental hygiene
Sleep	
High risk for sleep disturbances, obstructive and central sleep apnea	Monitor for sleep problems Refer for sleep study as indicated by history and before growth hormone initiation
Musculoskeletal	
Hip dysplasia	Newborn hip examination with appropriate referrals based on findings
Scoliosis (any age)	Monitor for scoliosis and kyphosis at visits (direct visual inspection and scoliometer); refer for radiographs, orthopedic care as indicated.
Kyphosis (in adolescence)	Imaging recommended before starting growth hormone, and annually in obese individuals
Development/behavior	
Developmental delay, cognitive impairment	Early intervention programming
Language delay	School programming
Food hoarding	Developmental-behavioral pediatrician or psychologist or child psychiatrist, depending on issues and community resources
Obsessive-compulsive features	
Skin picking	
Autism spectrum disorder	

- Through early identification, diagnosis, and implementation of behavioral strategies, hyperphagia and obesity can be decreased, thereby avoiding the complications of obesity.
- Increased awareness allows families to seek counseling and support for improved quality of life.
- Deaths.
  - Often the result of cardiorespiratory failure or complications of sleep apnea (cor pulmonale).
  - Reports of deaths from choking because of rapid food consumption.
  - Some sudden deaths in individuals may be explained by central adrenal insufficiency in times of stress.

BACKGROUND

- Optimum preoperative or procedural assessment often relies on the primary care physician to identify risk factors related to anesthesia and surgery.
- Ambulatory or same-day surgery provides significant medical, psychological, and economic benefits to children and their families.
- Administration of anesthesia and deep sedation increasingly are used in settings other than the operating room.
- The Pediatric Perioperative Cardiac Arrest (POCA) registry was created to study perioperative risks associated with cardiac arrest in children.
  - Of 397 perioperative cardiac arrests in children
    - 49% were anesthesia related.
    - 41% were related to cardiovascular issues.
    - 27% were caused by respiratory issues.
    - 18% were medication related.
  - Infants and patients with severe systemic diseases are at highest risk for perianesthetic mortality.

GOALS

- Goal of preoperative assessment is identification of potential risk factors and optimization of patient's clinical condition, particularly when there are complex medical problems.
- Avoidance of day-of-surgery cancellation benefits patients and physicians alike.

GENERAL APPROACH

American Society of Anesthesiologists Physical Status Classification

- Summarizes patient's physical condition and may provide a means of assessing relative risk of anesthesia (**Table 1**)

Trends and Statistical Information in Adverse Events

- POCA registry identifies trends in adverse events that occur in children receiving anesthetics and provides data on perioperative risk.
  - Infants and those children with severe systemic disease are at highest risk for perianesthetic mortality.
  - Most common cardiovascular causes of arrest are
    - Hemorrhagic hypovolemia
    - Metabolic consequences of massive blood transfusions
- Closed pediatric anesthesia malpractice claims registry allows evaluation of risk of adverse perioperative events.
  - Procedures most commonly cited
    - Dental, ear, nose, throat, maxillofacial procedures (36%)
    - Abdominal procedures (17%)
  - Suggests procedures related to the airways are associated with increased risk
- Incidence of adverse events is 75 per 1,000 anesthetics.
  - Most common events result from
    - Respiratory causes during the procedure
    - For younger children, respiratory adverse events in the recovery period as well
    - Vomiting during the recovery period

Nothing by Mouth: The Preoperative Fast

- Patients with large volumes of acidic gastric contents are at risk for pulmonary aspiration and significant morbidity.

P

Table 1. American Society of Anesthesiologists Physical Status Classification

Class	State	Cases
I	Healthy, normal child	
II	Child with mild systemic disease	Controlled asthma, controlled diabetes
III	Child with severe systemic disease	Active wheezing, diabetes mellitus with complications, heart disease that limits activity
IV	Child with severe systemic disease that is a constant threat to life	Status asthmaticus, severe BPD, sepsis
V	Child who is moribund and not expected to survive without the procedure	Cerebral trauma, pulmonary embolus, septic shock

Abbreviation: BPD, bronchopulmonary dysplasia.

Adapted from American Society of Anesthesiologists. ASA physical status classification system. http://asahq.org/resources/clinical-information/asa-physical-status-classification-system. Accessed April 26, 2017.

- Risk is less in pediatric patients, so practice of NPO (nil per os; nothing by mouth) after midnight has been abandoned.
- Current guidelines are shown in **Table 2.**
  - A 6-hour fast following a light meal is recommended; however, many pediatric anesthesiologists require a fast of 8 hours following solid food for elective procedures.
  - Clear liquids: water, clear fruit juices without pulp, carbonated beverages, clear tea, black coffee.

Perioperative Medication Management

- Medications to continue in the perioperative period, including day of surgery
  - β-blockers
  - Calcium channel blockers
  - Antiarrhythmics
  - Nitrates
  - Clonidine
  - Digoxin
  - Asthma medications (Care may even be escalated 1–2 weeks before surgery.)
    - β-agonists
    - Bronchodilators
    - Steroid inhalers
  - Seizure medications
  - Reflux medications
    - Proton pump inhibitors
    - H_2-receptor antagonists
  - Selective serotonin reuptake inhibitors
  - Insulin
  - Levothyroxine
  - Antithyroid agents
  - Glucocorticoids
  - Benzodiazepine
  - Opioids
  - Tricyclic antidepressants
  - Antipsychotics
- Medications to continue until the day before surgery but hold the day of surgery
  - Oral hypoglycemic agents
  - Diuretics
  - Angiotensin-converting enzyme inhibitors and angiotensin receptor blocking drugs
- Medications to discontinue preoperatively
  - Aspirin (7–10 days)
  - Nonsteroidal anti-inflammatory drugs (2–3 days)
  - Oral contraceptive pills (OCPs) (4–6 weeks) (Weigh decision against risk of unwanted pregnancy.)
  - Monoamine oxidase inhibitors (2 weeks)
  - Hormone replacement therapy (4–6 weeks, in conjunction with OCPs)
  - Herbal preparations (2 weeks [American Society of Anesthesiologists recommendations])
- Anticoagulants
  - Decision to stop or continue before surgery is governed by medical condition, indication for anticoagulation, and nature of procedure.
  - Consult surgeon, cardiologist, or other involved physicians to guide decision-making process.
  - Recommended time frames for discontinuation of medications that can alter hemostasis.
    - Aspirin (7 days)
    - Coumadin (5 days)
    - Clopidogrel (7 days)
    - Ticlopidine (10–14 days)
    - Dipyridamole (7 days)

SPECIFIC INTERVENTIONS

Preanesthetic History

- Focus on elements that may have consequences during anesthesia.
- Main concerns include pulmonary, cardiovascular, endocrine, hematologic, and neuromuscular systems.

P

Table 2. NPO (Nil Per Os; Nothing by Mouth) Guidelines

Ingested Material	Minimum Fasting Period
Clear liquids	2 h
Human (breast) milk	4 h
Infant formula	6 h
Nonhuman milk	6 h
Light meal	6 h

American Society of Anesthesiologists Committee on Standards and Practice Parameters. Practice guidelines for preoperative fasting and the use of pharmacologic agents to reduce the risk of pulmonary aspiration: application to healthy patients undergoing elective procedures: an updated report by the American Society of Anesthesiologists Committee on Standards and Practice Parameters. *Anesthesiology.* 2011;114(3):495–511.

- To determine risks, gather the following information:
  - Birth history: preterm versus full term, complications at birth, neonatal clinical course (respiratory, cardiovascular, neurologic issues)
  - Comorbidities and child's optimum clinical condition (eg, best pulmonary functions for a child with asthma on appropriate therapy)
  - Current acute illness (eg, upper respiratory infection, asthma exacerbation)
  - Developmental delays, autism spectrum disorder, or other behavioral-communicative disorders
  - Bleeding diathesis (eg, hemophilia, von Willebrand disease, sickle cell disease)
  - Allergies, especially to drugs, food, latex
  - Current and recent medications
  - Patient's weight
  - Previous surgical procedures and any adverse events
  - Previous anesthetics: ease or difficulty with intravenous (IV) access and airway instrumentation, complications
  - Family history of anesthesia complications
  - Family history of malignant hyperthermia
  - History of smoking, alcohol intake, substance abuse

Physical Examination

General

- Body habitus, height, weight (in kilograms)
- Vital signs: temperature, respiratory rate, heart rate, blood pressure
- Findings that raise concerns for anesthesia include
  - Morbid obesity
  - Limited mouth opening, recessed chin, short neck, large tongue, small mandible
  - Wheezing, ronchi, or rales on auscultation
  - Low baseline room air oxygen saturation
  - Presence of murmur
  - Cyanosis
  - Fever
  - Signs of severe dehydration/hypovolemia, including delayed capillary refill
  - Signs of increased intracranial pressure (eg, positional headaches, sundowning, recurrent vomiting, nystagmus)
  - Ill appearance
  - Poor weight gain
  - Excessive bleeding or bruising

Airway

- Examination of head and neck including
  - Mallampati classification
  - Mouth opening
  - Thyromental distance
  - Cervical range of motion
  - Mandibular or maxillary hypoplasia
  - Microsomia
  - Presence of loose teeth
- Conditions likely to be associated with a difficult airway
  - Pierre Robin sequence
  - Treacher Collins syndrome
  - Mucopolysaccharidosis
  - Down syndrome
  - Klippel-Feil syndrome
  - Choanal atresia (CHARGE syndrome)

Cardiovascular and Pulmonary

- Of particular importance because cardiovascular and respiratory systems undergo significant alterations under anesthesia.
- Thoroughly assess preoperative pulmonary and myocardial function.

Neuromuscular

- Assess type and extent of preexisting deficits.
- Baseline mental status, especially in nonverbal or developmentally delayed children.
  - Important in gauging responses during and after anesthesia
- Preexisting neuropathies and neurologic deficits should be documented to differentiate from possible complications.
  - Muscular dystrophies, myotonic dystrophia, congenital myotonia, and mitochondrial diseases may be associated with life-threatening conditions.

Preoperative Laboratory Evaluation

- Routine laboratory studies are not required for most procedures.
- Performed for specific conditions or high-risk procedures.
- Serum hemoglobin (Hb) or hematocrit (Hct) are the most commonly requested perioperative laboratory test.
  - Incidence of undetected anemia is extremely low (0.29%).
  - Unnecessary if results of studies performed as part of well-child care have been normal.
  - May be useful in
    - Chronic medical illness and procedure carries potential for significant blood loss.
    - Infants <6 months or who were born preterm.
    - African or African American children who have not had Hb or Hct determination after 6 months of age.

- Preoperative coagulation studies (prothrombin time, partial thromboplastin time, platelet count).
  - Useful in procedures with increased risk for intraoperative or postoperative bleeding, even when there is no history of bleeding disorder in patient or family
- Electrolytes.
  - Abnormalities of consequence are extremely rare in healthy children and routine preoperative testing is not indicated.
  - Serum electrolytes should be evaluated in children who
    - Have underlying conditions, such as renal insufficiency
    - Are taking diuretics, angiotensin-converting enzyme inhibitors, or other medications that may make an abnormal result more likely
    - Are limited to enteral feedings (nasogastric or gastrostomy tube) or parenteral nutrition
- Pregnancy.
  - Testing routine in many institutions for all menarcheal females or those >10 years
- Pulmonary function tests.
  - Rarely necessary in children with uncomplicated asthma
  - May be useful in predicting if children with pulmonary or thoracic cage abnormalities are at increased risk

Assessment and Management of Specific Conditions

Respiratory

- Upper respiratory tract infection (URTI) is a common condition that poses risk for complications including
  - Laryngospasm (can lead to negative-pressure pulmonary edema)
  - Bronchospasm (can make ventilation difficult)
  - Oxygen desaturation
  - Severe coughing
  - Breath holding
  - Post-extubation croup
  - Unplanned hospital admission
  - Prolonged need for mechanical ventilation
- Independent risk factors for adverse perianesthetic respiratory events with an active or recent URTI[1]
  - Age <5 years
  - Copious secretions
  - Endotracheal intubation required for procedure
  - History of reactive airway disease
  - History of preterm birth
  - Parental smoking history
  - URTI within the previous 4 weeks
  - Wet cough
  - Wheezing
- Asthma
  - Maximal preoperative optimization of patient's management can prevent or limit perioperative complications.
  - Escalate therapy preoperatively, even in asymptomatic patients or those who are well controlled.
    - Those who take asthma medications as needed should use their inhaled β-agonists or oral medications 3–5 days preoperatively.
    - Children on long-term medications (oral or inhaled) should have steroids added in doses normal for acute exacerbation.
    - Children with difficult-to-control asthma and who take bronchodilators and steroids regularly require intensification of therapy.
  - Elective surgery should never be performed in a child who is wheezing or who has had a recent asthma exacerbation.

Cardiovascular Disease

- Effects of general anesthesia on the cardiovascular system are more pronounced with underlying cardiac disease and can lead to hemodynamic instability and cardiovascular collapse.
- Signs and symptoms that may indicate serious underlying disease and warrant further investigation.
  - In infants
    - Diaphoresis with feeding or crying (times of increased cardiac demand)
    - Poor feeding
    - Tachypnea
    - Cyanosis/cyanotic spells
    - Failure to thrive, poor weight gain
    - Certain congenital syndromes
  - In older children
    - Poor exercise tolerance
    - Chest pain
    - Palpitations
    - Dyspnea on exertion
    - Family history of sudden deaths
  - Finding of a new murmur on examination (Most are innocent, and children are asymptomatic.)
- Children with suggestion of cardiac disease should undergo thorough cardiac evaluation before elective surgery.

- American Heart Association guidelines for prevention of infective endocarditis (IE)[2]
  - Bacteremia resulting from activities of daily living are more likely to result in IE than bacteremia from dental procedures.
  - Even if prophylaxis were completely effective, only an extremely small number of cases of IE may be prevented with antibiotic prophylaxis.
  - Recommendation of antibiotic prophylaxis is not based exclusively on increased lifetime risk of developing endocarditis.
  - Prophylaxis of IE is recommended only in patients with conditions that put them at the highest risk of adverse outcomes should they develop endocarditis.
  - Antibiotic prophylaxis is no longer recommended for patients with other forms of cardiac conditions not listed.
  - Antibiotic prophylaxis is recommended only for the dental procedures that involve manipulation of the gingival tissues or periapical tissue of teeth or perforation of the oral mucosa in patients with underlying high-risk cardiac conditions.
  - Antibiotic prophylaxis is recommended for procedures involving the respiratory tract or infected skin, skin structures, or musculoskeletal tissues only in patients with the underlying cardiac abnormalities outlined.
  - Antibiotic prophylaxis exclusively to prevent endocarditis is not recommended for gastrointestinal or genitourinary tract procedures.
  - The recommendation regarding the procedures for which endocarditis prophylaxis was not recommended in the 1997 guidelines remains in effect, including ear and body piercing, tattooing, vaginal delivery, and hysterectomy.
- Cardiac conditions associated with highest risk of adverse outcome from endocarditis for which prophylaxis with dental procedures is reasonable.[2]
  - Prosthetic cardiac valve or prosthetic material used for cardiac valve repair
  - Previous IE
  - Congenital heart disease (Except for the conditions listed previously, antibiotic prophylaxis is no longer recommended for any other form of congenital heart disease.)
    - Unrepaired cyanotic congenital heart disease, including palliative shunts and conduits
    - Completely repaired congenital heart defect with prosthetic material or device, whether placed by surgery or by catheter intervention, during the first 6 months after the procedure (Prophylaxis is reasonable because endothelialization of prosthetic material occurs within 6 months after the procedure.)
    - Repaired congenital heart disease with residual defects at the site or adjacent to the site of a prosthetic patch or prosthetic device (which inhibit endothelialization)
  - Cardiac transplantation recipients who develop cardiac valvulopathy

Preterm Neonates

- Neonates born at <37 weeks' gestation are at significant risk of apnea following sedative drugs or anesthetics.
  - Admit for monitoring following procedure.
  - Most apneic episodes occur within the first 2 hours but can occur for up to 12 hours.
  - Advisable to admit for 24 hours all patients with a post-conceptual age (gestational age added to age after birth) <60 weeks.
    - Recent studies suggest 50 weeks' postmenstrual age if specific risk factors are absent.
      - Prior history of apnea
      - Low gestational age
      - Very low birth weight
      - Low weight at time of surgery
      - Complicated neonatal course
  - Infants born at term must be ≥1 month for outpatient management.
    - Many centers and some states require infants to be 6 months of age for anesthesia in a freestanding ambulatory surgery center.

Down Syndrome

- Children with Down syndrome may be at increased risk of atlantoaxial instability (AAI).
  - Prevalence of AAI in Down syndrome is ~15%.
  - Atlantoaxial distance interval of >4–5 mm in any lateral view is abnormal.
    - A radiographic evaluation of the cervical spine is not accurate before 3 years of age; it is not recommended in asymptomatic children.

- High index of suspicion for AAI in a child with Down syndrome who presents with deterioration in motor skills, torticollis, and new-onset incontinence.
  - If the child has signs and symptoms indicating cervical spine instability or if the radiograph displays an atlantodens interval of >5 mm, elective surgery should be postponed and neurosurgical consultation sought.

- Cardiovascular anomalies occur in ~40%–50%; the most commonly associated heart defects are complete atrioventricular canal, ventricular septal defect, and atrial septal defect.
  - Echocardiogram should be performed.
  - Cardiology consultation when appropriate.
- Other anesthetic concerns include
  - Macroglossia, subglottic stenosis
  - Obstructive sleep apnea
  - Hypotonia
  - Hypothyroidism
  - Gastroesophageal reflux disease

Oncologic Disease

- Children with cancer typically require anesthetics for different procedures.
- Anesthetic concerns are based on type of cancer (**Table 3**) and effects of therapies (**Table 4**).

Endocrine Disease

- Patients with thyroid disease should have evaluation of thyroid-stimulating hormone and free thyroxine (T_4) levels.
  - Elective surgery should be postponed until euthyroid state is reached if levels are abnormal or there is clinical evidence of disease.
- Hypothyroidism.
  - Anesthetic concerns include
    - Cardiac: bradycardia, myocardial depression, hypotension, torsades de pointes
    - Sleep apnea: increased sensitivity to sedatives and narcotics
    - Blunted ventilatory response to hypoxia and hypercarbia
    - Respiratory muscle weakness
    - Airway obstruction resulting from macroglossia and obesity
    - Increased sensitivity to anesthetic agents
    - Slow drug metabolism (prolonged effects of anesthetic agents)
    - Hypothermia
    - Resistance to catecholamines
- Hyperthyroidism.
  - Anesthetic concerns include
    - Arrhythmias
    - Atrial fibrillation
    - Hypertension
    - Angina, ischemia
    - High-output cardiac failure
    - Exaggerated response to catecholamines
    - Thyroid storm
    - Goiter (may cause airway compromise)
      - Evaluate airway radiologically.
- Diabetes mellitus.
  - Goals of perioperative management are to avoid hyperglycemia and hypoglycemia.
    - Intensive insulin therapy to maintain normoglycemia has been associated with decreased infection and improved survival.
    - Risk of tight glycemic control is development of hypoglycemia; thus, close monitoring of serum glucose is required.
  - Preoperative assessment and preparation should include
    - Accurate documentation of pharmacologic regimen
    - Maintaining good glycemic control
    - Monitoring and recording occurrence of hypoglycemic episodes (frequency, severity)
  - Consider long-term complications of diabetes in preoperative evaluation.
  - Laboratory studies should include blood glucose, urea, creatinine, electrolytes, and urinalysis (for ketonuria).
    - HbA_{1c} measurement is not routine, but it is a good indicator of long-term glycemic control.
  - General principles for perioperative management of patients with diabetes.
    - Schedule as first cases of the day to minimize fasting period and disruption to treatment regimen.
    - Check blood glucose on arrival to the hospital; ideally should be <200 mg/dL.
      - Postpone elective surgery for levels >300 mg/dL.
    - Discontinue oral hypoglycemic agents preoperatively.
      - Stop metformin 48 hours before surgery and treat with subcutaneous short-acting insulin or sliding-scale insulin protocol.
    - Continue insulin in the perioperative period.

Table 3. Preoperative Considerations for Patients With Cancer

Physiologic Effects of Tumor	
Mass effect (anterior mediastinal mass, airway compromise)	Imaging studies (CT, MRI) needed
Tumor lysis syndrome (hyperkalemia, hyperphosphatemia, renal impairment, hypocalcemic seizures, metabolic acidosis, cardiac arrhythmia)	Hydration, correction of acidosis and electrolyte imbalance before elective procedures
Altered hemostasis	Check CBC, increased bleeding risk.
Effects of Chemotherapeutic Agents	
Bone marrow suppression	
• Anemia	Assess need for perioperative blood transfusion.
• Neutropenia	Immunocompromised state, increased infection risk, need for protective isolation, perioperative antibiotics
• Thrombocytopenia	Assess need for platelet transfusion, regional anesthesia may be contraindicated.
Cardiotoxicity	Obtain baseline and serial echocardiograms.
Pulmonary toxicity	Concern for hypoxia, chest radiograph
Nephrotoxicity	
Neurotoxicity	
Effects of Radiation Therapy	
Radiation therapy to the neck or oral cavity can render the airway difficult.	
Presence of Chronic Pain Syndromes and Analgesic Requirement	
Important to determine accurate doses of opioids and other medications used for neuropathic pain	Important to continue opioid analgesics and other medications (antidepressants, anticonvulsants) in the perioperative period to prevent withdrawal
Psychological Issues	
Depression, anxiety	Pharmacotherapy, counseling, support groups

Abbreviations: CBC, complete blood cell count; CT, computed tomography; MRI, magnetic resonance imaging.

Derived from Latham GJ, Greenberg RS. Anesthetic considerations for the pediatric oncology patient—part 1: a review of antitumor therapy. *Paediatr Anaesth.* 2010;20(4):295–304; Latham GJ, Greenberg RS. Anesthetic considerations for the pediatric oncology patient—part 2: systems-based approach to anesthesia. *Paediatr Anaesth.* 2010;20(5):396–420; Haberkern CM, Webel NE, Eisses MJ, Bender MA. Essentials of hematology. In: Coté CJ, Lerman J, Todres ID, eds. *A Practice of Anesthesia for Infants and Children.* 4th ed. Philadelphia, PA: Saunders Elsevier; 2009:177–194.

- Typically, morning insulin is halved on day of surgery, or sliding-scale insulin regimen is instituted along with IV infusion of 5% dextrose.
- Checking serum glucose is mandatory and guides management.
  - Insulin pumps are used increasingly; consultation with an endocrinologist may be necessary.
  - Blood glucose is checked at regular intervals during surgery and the postoperative period.

Table 4. Adverse Effects of Commonly Used Chemotherapeutic Agents

Chemotherapeutic Agent	Toxicity	Anesthetic Implications
Bleomycin	Pulmonary fibrosis	Important to elicit history of bleomycin use Obtain chest radiograph in high-risk patients. Check room air oxygen saturation. Avoid high Fio_2 concentration and fluid restriction in the perioperative period.
Busulfan	Pulmonary toxicity Hepatotoxicity	
Corticosteroids	Adrenal suppression, hypertension, obesity, hyperglycemia	Need for stress dose steroids perioperatively
Cisplatin	Nephrotoxicity Peripheral neuropathy	Check electrolytes. Document preexisting neurologic deficits.
Doxorubicin Daunorubicin	Cardiomyopathy	Baseline echocardiogram before initiating therapy and monitor serial echocardiograms. Cardiac consultation in high-risk patients Avoid cardio-depressant drugs.
Methotrexate	Myelosuppression Mucositis Hepatotoxicity	Check complete blood cell count. Increased risk of aspiration and airway compromise with mucositis
6-Mercaptopurine	Mucositis Hepatotoxicity	
Vinblastine Vincristine	Neurotoxicity, peripheral neuropathies SIADH	Document existing sensorimotor deficits to distinguish between neuropathies from positioning and complications of regional anesthesia

Abbreviations: Fio_2, fractional inspired oxygen; SIADH, inappropriate antidiuretic hormone secretion.

Derived from Haberkern CM, Webel NE, Eisses MJ, Bender MA. Essentials of hematology. In: Coté CJ, Lerman J, Todres ID, eds. *A Practice of Anesthesia for Infants and Children*. 4th ed. Philadelphia, PA: Saunders Elsevier; 2009:177–194; and Maxwell LG, Goodwin SR, Mancuso TJ, et al. Systemic disorders. In: Davis PJ, Cladis FP, Motoyama EK, eds. *Smith's Anesthesia for Infants and Children*. 7th ed. Philadelphia, PA: Mosby Elsevier; 2011:1064–1067.

Sickle Cell Disease

- Perioperative objectives in sickle cell disease
  - Thorough assessment to identify multisystem involvement.
    - History of acute chest syndrome
    - History of vasoocclusive pain crisis, hospitalizations
    - Neurologic assessment (hemiparesis, cognitive impairment)
    - History of chronic analgesic use and requirement
    - History of hematuria, renal insufficiency
  - Optimization of cardiopulmonary status.
    - Treatment of acute chest syndrome: hydration, supportive treatment, supplemental oxygen, aggressive bronchodilator therapy, antibiotics, chest physiotherapy, incentive spirometry, and, often, transfusion.

  - Hydroxyurea therapy and chronic transfusion therapy have been shown to decrease frequency of acute chest syndrome episodes.
    - Inhaled nitric oxide has been proved beneficial for acute management.
- Correction of anemia.
  - The National Institute of Health recommended (in 2002): "In patients with sickle cell disease-SS, simple transfusion to achieve hemoglobin of 10 g/dL should be performed before all but the lowest risk procedures."[3]
  - Very high risk patients may require a more aggressive transfusion approach.
    - Cerebrovascular disease occurs in ~8% of patients with sickle cell disease.
    - Transfusion programs aimed at maintaining HbS level below 30% reduce risk of recurrent stroke from 60%–70% to <10%.[4]
    - Children at high risk for cerebrovascular accidents are usually maintained on chronic intermittent transfusions; this regimen should be continued in the perioperative period.
- Prevention of vasoocclusive crisis.
  - Prolonged fasting should be avoided to prevent dehydration and subsequent vascular stasis that can promote sickling.
  - Ideally, these patients should be admitted before surgery and IV hydration initiated during the fasting period.
  - Optimize analgesia: A strategy for pain control should be devised, and pediatric pain service (if available) should be involved early, especially in those with frequent pain crisis.
- Any ongoing infections should be treated before elective procedures.

■ High-risk patients with sickle cell disease
- Sickle cell chronic lung disease
- Frequent acute chest syndrome
- Reactive airway disease
- Abnormal chest radiograph
- Abnormal pulmonary function test
- History of stroke
- High transcranial Doppler velocity
- On chronic transfusion protocols

■ Investigations for high-risk patients
- Complete blood cell count: baseline Hb and Hct
- Chest radiography
- Pulmonary function tests
- Electrocardiogram (ECG)
- Echocardiogram
- Serum blood urea nitrogen and creatinine
- Neurologic imaging
- Liver function tests

Mitochondrial Myopathies

■ Mitochondrial syndromes encountered include
- Leigh disease
- Kearns-Sayre syndrome
- Leber hereditary optic neuropathy

■ Clinical features include myopathy, cardiomyopathy, encephalopathy, seizures, cerebellar ataxia, and gastrointestinal symptoms.

■ Anesthetic considerations.
- Respiratory muscle weakness
  - Increased sensitivity to volatile anesthetics and narcotic medications predisposes to the development of postoperative respiratory insufficiency.
- Cardiomyopathy
  - Warrants judicious use of agents that can further depress myocardial function
  - Preoperative assessment of cardiac function with echocardiogram and cardiac consultation as required
- Cardiac conduction defects
  - Baseline ECG preoperatively.
  - Drugs with arrhythmogenic potential should be avoided intraoperatively.
- Avoid prolonged fasting that can lead to exaggerated metabolic response causing acidosis.
  - IV hydration with glucose-containing fluids should be initiated while the patient is NPO to avoid anaerobic metabolism.
  - Avoid lactated Ringer injection to prevent additional lactate load.
- Maintain normothermia.
  - Shivering can have deleterious effects on the compromised cellular metabolism.
  - Hyperthermia is also undesirable.
- Maintain Hct near normal levels to ensure adequate oxygen delivery.
- Avoid hypotension and hypoxia.
- Pain can increase sympathetic tone, leading to increased oxygen demand.
  - Appropriate pain management as necessary.

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Preparticipation Physical Evaluation

BACKGROUND

- >7 million high school students participate in sports each year.
- Preparticipation Examination Task Force.
  - Formed in the early 1990s by the American Academy of Family Physicians, American Academy of Pediatrics (AAP), American College of Sports Medicine, American Medical Society for Sports Medicine, American Orthopaedic Society for Sports Medicine, and American Osteopathic Academy of Sports Medicine
  - Released preparticipation physical evaluation (PPE) guidelines in 1992; updated in 1997, 2002, 2004, and 2010
    - Guidelines are the basis for current PPE.
    - PPE is one of the most commonly performed examinations.
- PPE has evolved to allow physicians to provide consistent, high-quality examinations nationwide.

GOALS

- The purpose of the PPE is to promote the health and safety of the young athlete in training and competition.
- Because pediatricians should counsel all patients to be physically active, the definition of *athlete* should include all pediatric patients.
- Primary goals of the PPE are to
  - Detect conditions that might predispose the athlete to injury.
    - Musculoskeletal history and physical examination are the best ways to discover orthopedic problems.
  - Detect conditions that might be life-threatening or disabling.
    - Sudden cardiac death in young athletes is rare, but a history of syncope or chest pain with exercise or family history of sudden death <50 years should be evaluated.
    - Topics that must be discussed and emphasized include
      - Concussion
      - Heat injury
      - Use of nutritional supplements
  - Meet legal or insurance requirements.
- Secondary goals are to
  - Determine general health.
  - Counsel athletes on health-related issues.
  - Update medications and immunizations.
  - Create a medical home.
  - Assess fitness level.
- Identifying athletes who may need further diagnostic testing, counseling, or rehabilitation is the primary goal of PPE, but many other expectations exist.
  - Parental expectations
    - May expect PPE to be a comprehensive evaluation of athlete's health, including areas unrelated to sports participation (eg, teenage sexuality, substance abuse, immunizations)
    - Often think of PPE as comprehensive and the only medical evaluation a child or adolescent needs
  - Physicians often view PPE as a cursory examination intended only to detect conditions that might limit or impair athletic endeavors.
  - Because parents and physicians may view PPE differently, the intent, scope, and purpose of the examination must be made clear to parents.

GENERAL APPROACH

- PPE typically is conducted by 1 of 2 methods.
  - Station method
    - Divides examination into several components.
      - Physicians, nurses, athletic trainers, and coaches are each assigned to a single task.
    - Ideally suited for screening large numbers of athletes.
    - Benefits are relative efficiency and good ability to identify abnormalities.
      - Affords less rapport with athletes and offers no privacy
    - Athletes have little opportunity to ask questions about their health or other medical or personal issues.
  - Office-based method
    - Has the advantage of an established physician-patient relationship.
      - The athlete's medical history is known, and continuity of care is fostered.
    - Disadvantages include lack of consistency among physicians, potential physician unfamiliarity with the sport and its disqualifying conditions, and lack of cost-effectiveness.
    - Routine laboratory studies and radiographs are not generally performed.
    - Based on information obtained during history and physical examination, further studies may be indicated.
- Ideally, all steps in the PPE should be performed by a single physician, even if mass screening is taking place.

- Timing.
  - PPE should be performed
    - Early enough before the sport's season begins to ensure that athletes with medical problems can be thoroughly evaluated and treated
    - Not so early that intervening injuries are likely to occur
  - The best time for evaluation is 6 weeks before the first scheduled practice.
    - Allows time for thorough evaluation, consultations, and rehabilitation of any identified musculoskeletal injuries
  - Current AAP guidelines suggest that PPE should be performed every year.
    - Other sources suggest that PPE be conducted before the beginning of each new level of competition (ie, junior high, high school), with annual updates of history and targeted physical examinations of areas of concern.
  - Most state high school athletic associations require annual evaluations.
    - A recent survey found that 65% of states require annual examination for all athletes competing in high school sports.
- History.
  - Identifies most potential problems for young athletes.
  - Despite best screening of athletes with intent of preventing sudden death, only a few who die would have been detected through history and physical examination.
    - Cardiovascular and musculoskeletal examinations identify most athletes who warrant further evaluation or disqualification.
    - The key to identifying problems is the questionnaire that systematically screens for conditions that might cause problems or lead to sudden death during athletic activity.
  - **Table 1** lists some of the most important questions to ask during the examination.
- PPE forms provided by state high school athletic associations often do not incorporate all the screening questions recommended by the Preparticipation Examination Task Force.
- Athletes typically complete history forms without input from parents.
  - A study showed that only 40% of PPE forms matched when filled out independently by parent and child.
  - The athlete and his or her parents should complete the form together to obtain a thorough and accurate history.
  - Some issues may arise (particularly when the practice is the medical home) in which adolescent privacy on certain topics should be respected.
- Sports are classified based on the likelihood of collision injury and strenuousness of the exercise.
  - These classifications are used to guide physicians on risk of injury and degree of cardiopulmonary fitness required to engage in the sport successfully.
  - The AAP has established classification guidelines by intensity (**Table 2**) and level of contact.
- Clearance to play.
  - Few athletes are disqualified from activity on the basis of conditions identified during PPE.
    - **Table 3** lists the most current recommendations on medical conditions and contraindications to participation.
    - Working with athletes to find safe, enjoyable sports in which they can participate is important.
    - If possible, and depending on the condition detected, sports participation should not be eliminated altogether.

SPECIFIC INTERVENTIONS

Physical Examination

General

- 2 key components (cardiovascular and musculoskeletal) identify most athletes who warrant further evaluation or disqualification.

Cardiovascular Examination

- **Table 4** lists indications for preparticipation cardiovascular screening.
- Include evaluation of peripheral pulses, murmurs, and blood pressure.
  - All diastolic murmurs and grade 3/6 systolic murmurs warrant further evaluation.
  - Hypertrophic cardiomyopathy.
    - One of the most important conditions to detect
    - May produce a systolic murmur indistinguishable from an innocent murmur; murmur of hypertrophic cardiomyopathy
      - Increases in intensity with a Valsalva maneuver (decreased ventricular filling, increased obstruction)
      - Decreases with squatting (increased ventricular filling, decreased obstruction)
      - Increases in intensity when the athlete moves from squatting to standing position

(continued on page 915)

Table 1. Medical History Questions

	Question	Reason
1	Injury or illness since last checkup?	Targets potential physical examination concerns
2	Chronic illnesses, hospitalizations, or surgeries?	Identifies potential counseling or rehabilitation issues
3	Any medications or supplements of any type?	Identifies drugs that may inhibit or interfere with sports participation
4	Allergies to medications, insects, or food?	Alerts physicians and trainers for potential allergic reactions
5	Dizziness, passing out, chest pain with exercise? History of sudden death in a close relative?	Identifies potential causes of sudden death caused by cardiovascular problems
6	Have you ever passed out or nearly passed out during exercise? Have you ever passed out or nearly passed out after exercise? Have you ever had discomfort, pain, or pressure in your chest during exercise? Does your heart race or skip beats during exercise? Does anyone in your family have Marfan syndrome?	Targets cardiovascular concerns
7	Ever been restricted from sports by a physician?	Identifies potential disqualifying problems
8	Any skin problems?	Identifies potential transmittable disease during contact
9	Concussion, knocked out, unconsciousness, memory loss, seizure, or severe or frequent headache?	Targets neurologic concerns
10	Stinger, burner, pinched nerve, numbness or tingling in extremities?	Targets neurologic concerns
11	Problems while exercising in the heat?	Targets heat illness concerns
12	Asthma, allergies, wheezing, difficulty breathing, or chest pain?	Identifies potential for exercise-induced asthma
13	Special equipment or devices not usually used in your sport?	Identifies potential concerns for physician follow-up
14	Glasses, contacts, or vision or eye problems?	Identifies ophthalmologic concerns
15	Strain, sprain, fracture, joint pain, or swelling?	Identifies potential musculoskeletal problems
16	Concerns about weight: Do you lose weight regularly for your sport?	Identifies potential disordered eating

Table 1 (*continued*)

	Question	Reason
17	Feel stressed out?	Clue to ask follow-up questions about drug use, eating problems, sexuality, and home and school problems
18	Recent immunizations (tetanus, measles, hepatitis B, chickenpox, whooping cough, HPV, meningitis)?	Health maintenance issues
19	Girls only: menstrual history?	Identifies oligomenorrhea and amenorrhea and potential risk for poor nutrition, stress fractures
20	Do you wear protective braces, splints?	Identifies injuries that have not been fully rehabilitated

Abbreviation: HPV, human papillomavirus.

Table 2. Sports Classification by Intensity

High-to-Moderate Intensity High-to-Moderate Dynamic High-to-Moderate Static Demands	High-to-Moderate Intensity High-to-Moderate Dynamic Low Static Demands	High-to-Moderate Intensity Low Dynamic High-to-Moderate Static Demands	Low Intensity Low Dynamic Low Static Demands
Boxing	Badminton	Archery	Bowling
Crew rowing	Baseball	Auto racing	Cricket
Cross-country skiing	Basketball	Diving	Curling
Cycling	Field hockey	Equestrian	Golf
Downhill skiing	Lacrosse	Field events (eg, jumping, throwing)	Rifle shooting
Fencing	Orienteering	Gymnastics	
Football	Table tennis	Karate or judo	
Ice hockey	Race walking	Motorcycling	
Rugby	Racquetball	Rodeo	
Running (sprint)	Soccer	Sailing	
Speed skating	Squash	Ski jumping	
Water polo	Swimming	Water skiing	
Wrestling	Tennis	Weight lifting	
	Volleyball		

Adapted from Rice SG; American Academy of Pediatrics Council on Sports Medicine and Fitness. Medical conditions affecting sports participation. *Pediatrics.* 2008;121(4):841–848. Reaffirmed June 2014.

Table 3. Medical Conditions and Sports Participation

Condition	Participate?	Explanation
Atlantoaxial instability (instability of the joint between cervical vertebrae 1 and 2)	Qualified yes	Athlete needs evaluation[a] to assess risk of spinal cord injury during sports participation.
Bleeding disorder	Qualified yes	Athlete needs evaluation.
Carditis (inflammation of the heart)	No	Carditis may result in sudden death with exertion.
Hypertension (high blood pressure)	Qualified yes	Persons with significant essential (unexplained) hypertension should avoid weight lifting and power lifting, bodybuilding, and strength training. Those with secondary hypertension (hypertension caused by a previously identified disease) or severe essential hypertension need evaluation.
Congenital heart disease (structural heart defects present at birth)	Qualified yes	Persons with mild forms may participate fully; those with moderate or severe forms or who have undergone surgery need evaluation.
Dysrhythmia (irregular heart rhythm)	Qualified yes	Athlete needs evaluation because some types require therapy or make certain sports dangerous, or both.
Mitral valve prolapse (abnormal heart valve)	Qualified yes	Persons with symptoms (chest pain, symptoms of possible dysrhythmia) or evidence of mitral regurgitation (leaking) on physical examination need evaluation. All others may participate fully.
Heart murmur	Qualified yes	If the murmur is innocent (does not indicate heart disease), full participation is permitted; otherwise, the athlete needs evaluation (see "Congenital heart disease" and "Mitral valve prolapse").
Cerebral palsy	Qualified yes	Athlete needs evaluation.
Diabetes mellitus	Yes	All sports can be played with proper attention to diet, hydration, and insulin therapy. Particular attention is needed for activities that last ≥30 minutes.
Diarrhea	Qualified no	Unless disease is mild, no participation is permitted because diarrhea may increase the risk of dehydration and heat illness. See "Fever."
Eating disorders, anorexia nervosa, bulimia nervosa	Qualified yes	These patients need medical and psychiatric assessment before participation.
Eyes: functionally one-eyed athlete, loss of an eye, detached retina, previous eye surgery, or serious eye injury	Qualified yes	A functionally one-eyed athlete has a best-corrected visual acuity of <20/40 in the worse eye. These athletes would experience significant disability if the better eye were seriously injured, as would those with loss of an eye. Some athletes who have previously undergone eye surgery or had a serious eye injury may have an increased risk of injury because of weakened

Table 3 (*continued*)

Condition	Participate?	Explanation
Eyes (*continued*)		eye tissue. Availability of eye guards approved by the American Society for Testing Materials and other protective equipment may allow participation in most sports, but this determination must be made on an individual basis.
Fever	No	Fever can increase cardiopulmonary effort, reduce maximal exercise capacity, make heat illness more likely, and increase orthostatic hypotension during exercise. Fever may rarely accompany myocarditis or other infections that may make exercise dangerous.
History of heat illness	Qualified yes	Because of the increased likelihood of recurrence, the athlete needs individual assessment to determine the presence of predisposing conditions and to arrange a prevention strategy.
HIV infection	Yes	Because of the apparent minimal risk to others, all sports may be played that the state of health allows. In all athletes, skin lesions should be properly covered, and athletic personnel should use universal precautions when handling blood or body fluids with visible blood.
Kidney: absence of one	Qualified yes	Athlete needs individual assessment for contact or collision and limited contact sports.
Liver: enlarged	Qualified yes	If the liver is acutely enlarged, participation should be avoided because of risk of rupture. If the liver is chronically enlarged, individual assessment is needed before collision or contact or limited contact sports are played.
Malignancy	Qualified yes	Athlete needs individual assessment.
Musculoskeletal disorders	Qualified yes	Athlete needs individual assessment.
History of serious head or spine trauma, severe or repeated concussions, or craniotomy	Qualified yes	Athlete needs individual assessment for collision or contact or limited contact sports and for noncontact sports if deficits exist in judgment or cognition. Recent research supports a conservative approach to management of concussions.
Convulsive disorder (well controlled)	Yes	Risk of convulsion during participation is minimal.
Convulsive disorder (poorly controlled)	Qualified yes	Athlete needs individual assessment for collision or contact or limited contact sports. Avoid the following noncontact sports: archery, rifle shooting, swimming, weight lifting or power lifting, strength training, or sports involving heights. In these sports, occurrence of a convulsion may be a risk to self or others.

Table 3 (*continued*)

Condition	Participate?	Explanation
Obesity	Qualified yes	Because of the risk of heat illness, obese persons need careful acclimatization and hydration.
Organ transplant recipient	Qualified yes	Athlete needs individual assessment.
Ovary: absence	Yes	Risk of severe injury to the remaining ovary is minimal.
Respiratory, pulmonary compromise (including cystic fibrosis)	Qualified yes	Athlete needs individual assessment, but, generally, all sports may be played if oxygenation remains satisfactory during a graded exercise test. Patients with cystic fibrosis need acclimatization and good hydration to reduce the risk of heat illness.
Asthma	Yes	With proper medication and education, only athletes with the most severe asthma will have to modify their participation.
Acute upper respiratory infection	Qualified yes	Upper respiratory obstruction may affect pulmonary function. Athlete needs individual assessment for all but mild diseases. See "Fever."
Sickle cell disease	Qualified yes	Athlete needs individual assessment. In general, if status of the illness permits, all but high-exertion, collision, or contact sports may be played. Overheating, dehydration, and chilling must be prevented.
Sickle cell trait	Yes	Individuals with sickle cell trait do not likely have an increased risk of sudden death or other medical problems during athletic participation except under the most extreme conditions of heat and humidity and possibly high altitude. These individuals, as with all athletes, should be carefully conditioned, acclimatized, and hydrated to reduce any possible risk.
Skin: boils, herpes simplex, impetigo, scabies, molluscum contagiosum	Qualified yes	Because the patient is contagious, participation in gymnastics with mats, martial arts, wrestling, or other collision or contact or limited contact sports is not allowed. Herpes simplex is probably not transmitted via mats.
Spleen: enlarged	Qualified yes	Persons with acutely enlarged spleens should avoid all sports because of risk of rupture. Those with chronically enlarged spleens need individual assessment before playing collision or contact or limited contact sports.
Testicle: absent or undescended	Yes	Certain sports may require a protective cup.

[a] "Needs evaluation" means that a physician with appropriate knowledge and experience should assess the safety of a given sport for an athlete with the listed medical condition. Unless otherwise noted, this term is used because of the variability of the severity of the disease, the risk of injury among the specific sport, or both.

Adapted from Rice SG; American Academy of Pediatrics Council on Sports Medicine and Fitness. Medical conditions affecting sports participation. *Pediatrics.* 2008;121(4):841–848. Reaffirmed June 2014.

Table 4. Cardiovascular Screening in Athletes

Condition	Cardiovascular Examination	Abnormality
Hypertension	Blood pressure	Varies with age; general guideline is >135/85 mm Hg in adolescents.
Coarctation of aorta	Femoral pulses	Decreased intensity of pulse
Hypertrophic cardiomyopathy	Auscultation with provocative maneuvers (standing, supine, Valsalva maneuver)	Systolic ejection murmur that intensifies with standing or Valsalva maneuver
Marfan syndrome	Auscultation	Aortic (decrescendo diastolic murmur) or mitral insufficiency (holosystolic murmur)

Derived from Maron BJ, Thompson PD, Puffer JC, et al. Cardiovascular preparticipation screening of competitive athletes. A statement for health professionals from the Sudden Death Committee (clinical cardiology) and Congenital Cardiac Defects Committee (cardiovascular disease in the young), American Heart Association. *Circulation*. 1996;94(4):850–856.

- Blood pressures obtained during PPE often are high.
  - Blood pressure cuff may be too small, particularly in large adolescents.
    - Athlete's blood pressure truly is high when age-based reference ranges are consulted.
  - Hypertension rarely is severe enough to disqualify an athlete from participation, but it must be identified and monitored by the athlete's regular physician.
  - Weight-training activities should be restricted in patients who have severe hypertension.
- Sudden cardiac death.
  - Rare in young athletes; however, history of syncope, chest pain with exercise, or family history of sudden death <50 years should be evaluated.
  - Positive response to the cardiac history questions detailed in the PPE monograph and history form warrants further evaluation.
  - Recent research showed that screening for sudden cardiac death that included standardized history, physical examination, and electrocardiography may have helped prevent sudden death caused by cardiomyopathy.

- Diagnostic testing (eg, electrocardiograms) still not universally accepted as standard of care, due to
  - Low positive predictive value
  - Lack of trained or expert clinicians adept at interpreting electrocardiograms in athletes
  - Cost

Musculoskeletal Examination

- Typically accounts for 50% of abnormal physical findings on PPE.
- Should focus on previously injured or symptomatic areas.
- 92% of orthopedic injuries are detected by history alone.
- Some authorities suggest a sport-specific approach, focusing on most common injuries for each sport.
- Special considerations for examination of injured or symptomatic joints include
  - Inspection for visual deformity, muscle mass, asymmetry, and swelling
  - Palpation for localized areas of tenderness, warmth, and effusion
  - Assessment of range of motion (eg, with hip pain test for loss of internal rotation and abduction, which can be seen in slipped capital femoral epiphysis and Legg-Calvé-Perthes disease)
  - Evaluation of neurovascular status through muscle strength, sensation, reflexes, and pulses of involved limb (eg, an athlete with a history of burners should undergo complete neurovascular testing of the neck and upper extremities)
  - Evaluation of joint stability (eg, an athlete with knee pain should undergo tests for valgus and varus stress, Lachman test, and posterior drawer test)

Laboratory Studies

- Have not been shown to be cost-effective or warranted in young asymptomatic athletes.
- Routine urinalysis and hematocrit for all athletes have been largely abandoned.
  - Do not identify athletes who require disqualification.
  - Have a high rate of false-positive results.
- Electrocardiography, echocardiography, and stress testing are not suggested to screen asymptomatic individuals because of high false-positive rate and high cost.

Special Considerations

- Nutritional supplements
  - Sports supplements have become a billion-dollar industry.
    - Athletes as young as 11 years are taking performance-enhancing supplements.
    - PPE is the ideal time to question athletes briefly about supplement use.
    - Sports supplements contain impurities; when taken inappropriately, they may result in adverse side effects.
      - Muscle cramps
      - Dehydration
      - Abdominal bloating
      - Tachycardia
      - Arrhythmia
      - Death
    - Supplement use should be discouraged; young athletes should be told about their possible ill effects.
- Obesity
  - Up to 30% of children are obese.
  - Obesity is not a contraindication to sports participation unless a comorbid finding, such as severe hypertension, is present.
  - Obese children are at increased risk of heat injury and should be counseled accordingly.
  - Sports participation with emphasis on activities that improve fitness should be encouraged.
- Concussion
  - History of concussion should be addressed during PPE.
  - Consensus related to concussion management continues to evolve.
  - Concussion should be thoroughly evaluated by a sports medicine professional or neurologist if it
    - Requires a long time for recovery
    - Involves significant amnesia, prolonged loss of consciousness, or seizure
  - Neuropsychological testing is suggested with repeat or complicated concussion.
  - Patients must meet 3 criteria to return to play after concussion.
    - Asymptomatic at rest
    - Asymptomatic with exercise
    - No neurocognitive deficits (eg, memory loss, concentration problems, fatigue, fogginess, confusion)
- Medical home
  - Adolescents are the most underserved population in health care today.
    - In many instances, their only contact with the medical system is PPE.
    - All young athletes should be referred to their pediatric primary care physician for routine care and for follow-up of any ongoing medical conditions.

DEFINITION

- Infection of tissues anterior to the orbital septum is described as a *preseptal* or *periorbital* infection.
  - The terms *preseptal* and *periorbital* may be used interchangeably.
  - Preseptal cellulitis, or periorbital cellulitis, is an inadequate diagnostic label unless accompanied by a modifier that indicates the probable pathogenesis.
- Orbital cellulitis is infection of the soft tissues of the orbit posterior to the orbital septum.

SIGNS AND SYMPTOMS

Preseptal Cellulitis Infections After Trauma

- Loosely bound periorbital soft tissues permit impressive swelling to accompany minor infection.
- Overlying skin can be bright red with subtle textural changes.
- Intense swelling can lead to shininess.
- Ulceration and vesicle formation in the presence of ringworm.
- Some patients have fever.
- Many are afebrile despite dramatic local findings.
- Peripheral leukocyte count is variable.

Bacteremic Periorbital Cellulitis

- Age <18 months.
- History of viral upper respiratory infection (URI) for several days.
- Sudden increase in temperature (to >39.0°C [102.2°F]).
- Acute onset and rapid progression of eyelid swelling.
  - Swelling usually begins in the inner canthus of the upper and lower eyelid.
  - Can obscure the eyeball within 12 hours.
- Markedly discolored and erythematous periorbital tissues.
- If swelling has been rapidly progressive, the area may have violaceous discoloration.
- The child's resistance to examination commonly leads to an erroneous impression of tenderness.
- Retraction or separation of the eyelids reveals that
  - The globe is normally placed.
  - Extraocular eye movements are intact.
- The young age of patients, high fever, and rapid progression of findings differentiate bacteremic preseptal cellulitis from other causes of swelling around the eye.
- Bacteremic cellulitis rarely arises from the paranasal sinus cavities.
  - Typable *Haemophilus influenzae* organisms are rarely recovered from maxillary sinus aspirates.
  - Typable *H influenzae* organisms are rarely recovered from abscess material in patients who have serious local complications of paranasal sinus disease (eg, subperiosteal abscess).
  - *Streptococcus pneumoniae* can cause subperiosteal abscess in patients with acute sinusitis.
    - Such patients are not usually bacteremic.

Preseptal (Periorbital) Cellulitis Caused by Inflammatory Edema of Sinusitis

- Several complications of paranasal sinusitis can result in swelling around the eye.
- The most common and least serious complication is often called *inflammatory* edema or *sympathetic effusion*.
- Typical patient is
  - ≥2 years
  - Has had viral URI for several days when swelling is noted
- History of intermittent early morning periorbital swelling that resolves after a few hours.
- On the day of presentation, eyelid swelling does not typically resolve but progresses gradually.
- Striking degrees of erythema can also be present.
- Eye pain and tenderness are variable.
- Eyelids can be very swollen and difficult to evert, requiring the assistance of an ophthalmologist.
- When the ethmoid sinuses are completely congested, venous drainage is physically impeded.
  - Results in soft-tissue swelling of the eyelids, maximal at the medial aspect of the lids.
  - Infection is confined within the paranasal sinuses.
- No displacement of the globe or impairment of extraocular eye movements.
- Fever, if present, is usually low grade.
- Peripheral leukocyte count is unremarkable.
- Blood culture results are always negative.
- If a tissue aspiration is performed, culture of specimen has a negative result.
- Sinus radiographs show ipsilateral ethmoiditis or pansinusitis.
- The following factors differentiate inflammatory edema from bacteremic periorbital cellulitis:
  - Age of the child
  - Gradual evolution of lid swelling
  - Modest temperature elevation

True Orbital Disease Secondary to Sinusitis

- Orbital infection is the least common cause of a swollen eye.
- Sudden onset of erythema and swelling about the eye.
- Preceded by several days of a viral URI.
- Eye pain can precede swelling and is often dramatic.
- Presence of fever, systemic signs, and toxicity is variable.
- Orbital infection is suggested by
  - Proptosis (with the globe displaced usually anteriorly and downward)
  - Impairment of extraocular eye movements (most often upward gaze)
  - Chemosis (edema of the bulbar conjunctiva) *or*
  - Loss of visual acuity or decreased pupillary reaction (late in the evolution of the infection)

DIFFERENTIAL DIAGNOSIS

- Young age, high fever, and rapid progression of findings differentiate bacteremic preseptal cellulitis from other causes of swelling around the eye.
- Noninfectious causes include
  - Blunt trauma (resulting in a black eye).
    - History provides the key to diagnosis.
    - Eyelid swelling continues to increase for 48 hours and then resolves over several days.
  - Tumors that characteristically involve the eye include
    - Hemangioma of the lid
    - Ocular tumors, such as
      - Retinoblastoma
      - Choroidal melanoma
    - Orbital neoplasms, such as
      - Neuroblastoma.
      - Rhabdomyosarcoma.
      - Langerhans cell histiocytosis.
      - Tumors usually cause gradual onset of proptosis in the absence of inflammation.
  - Orbital pseudotumor.
    - Autoimmune inflammation of orbital tissues, which exhibits
      - Eyelid swelling
      - Red eye
      - Pain
      - Decreased ocular motility
  - Hypoproteinemia and congestive heart failure cause eyelid swelling as a result of local edema.
    - Characteristic findings are bilateral, boggy, nontender, non-discolored soft-tissue swelling.
  - Allergic inflammation.
    - Includes angioneurotic edema or contact hypersensitivity
      - Superficially, these problems can resemble findings in acute infection.
      - However, presence of pruritus and absence of tenderness are helpful distinguishing characteristics of allergic inflammation.
- Infectious causes include
  - Orbital infections
    - Subperiosteal abscess.
    - Orbital abscess.
    - Orbital cellulitis.
    - Cavernous sinus thrombosis.
    - Traumatic inoculation.
    - Endophthalmitis.
    - In young children, ethmoiditis and ethmoid osteitis.
    - In adolescents, frontal sinusitis and osteitis.
    - Patients with diabetes and immunocompromised children are at higher risk of fungal orbital cellulitis (especially *Mucor* species).

DIAGNOSTIC APPROACH

- Detailed history of onset and progression of swelling helps distinguish infectious from noninfectious causes.
- The child with a swollen eye is commonly seen in primary care.
- Approach to diagnosis depends on physical examination.

LABORATORY FINDINGS

- Preseptal cellulitis infections after trauma
  - Peripheral leukocyte count is variable.
- Bacteremic periorbital cellulitis
  - A precise bacteriologic diagnosis is made by recovery of the organism from blood culture.
- Preseptal (periorbital) cellulitis caused by inflammatory edema of sinusitis
  - Peripheral leukocyte count is unremarkable.
  - Blood culture results are always negative.

IMAGING

- Bacteremic periorbital cellulitis.
  - Radiographs of the paranasal sinuses are often abnormal.
    - Abnormalities almost certainly reflect the viral respiratory syndrome that precedes and probably predisposes the patient to the bacteremic event rather than clinically significant sinusitis.
  - If retraction of the lids is not possible, orbital computed tomography (CT) may be necessary.
- Orbital infections.
  - Imaging studies
    - Are usually performed if orbital disease is suspected.
    - Help determine cause of the clinical findings.
      - Subperiosteal abscess
      - Orbital abscess
      - Orbital cellulitis
- On occasion, CT results can be misleading.
  - They may suggest abscess when inflammatory edema is present.

DIAGNOSTIC PROCEDURES

- Preseptal cellulitis infections after trauma
  - Patients with bacterial cellulitis of traumatized areas rarely have bacteremia.
  - The precise bacteriologic diagnosis is made through culture of exudate from the wound.
  - If there is no drainage, tissue aspiration is carefully attempted.
    - Perform only if it can be done safely (ie, at a distance far enough from the orbit that no potential damage to the eye can occur).
    - Tuberculin syringe with a 25-gauge needle can be used for aspiration.
    - Usually, only a minuscule amount of infected material can be aspirated.
    - Small volume of non-bacteriostatic saline (0.2 mL) is drawn into the syringe before the procedure.
      - Not injected into skin
      - Used to expel a small volume of tissue fluid onto chocolate agar for culture
- Bacteremic periorbital cellulitis
  - If tissue aspiration is performed, culture of specimen may have a positive result.
  - Lumbar puncture should be performed unless the clinical picture precludes meningitis.
- Preseptal (periorbital) cellulitis caused by inflammatory edema of sinusitis
  - If tissue aspiration is performed, specimen culture result is negative.

CLASSIFICATION

- Preseptal
  - Infections: due to local trauma or spread from local infectious site
- Bacteremic preseptal
  - Inflammatory: due to inflammatory swelling secondary to sinusitis
- Orbital

TREATMENT APPROACH

- Practitioners frequently need to manage the child whose chief symptom is a swollen eye.
  - Some are trivial or self-limited disorders, such as allergic reaction.
  - Others are sight- or life-threatening problems, especially infectious.
- If orbital disease is suspected, the clinical course is the ultimate guide to management.

SPECIFIC TREATMENTS

Preseptal Cellulitis Infections After Trauma

- Treat aggressively to prevent cavernous sinus thrombosis.
- After local cultures are obtained, initiate vancomycin at 15 mg/kg/dose every 6 hours in communities where methicillin-resistant *Staphylococcus aureus* is prevalent.
  - For other organisms, intravenous (IV) treatment tailored to the isolate.
  - Oral therapy can be used to complete a 10-day course of treatment after substantial improvement.

Bacteremic Periorbital Cellulitis

- Uncommon since introduction of conjugate vaccines for *H influenzae* type b and *S pneumoniae.*
- Requires parenteral therapy.
- *S pneumoniae* is the most likely cause in a child who received the *H influenzae* type b and pneumococcal conjugate vaccine series.
- Infection is usually bacteremic in the age group in which the meninges are susceptible to inoculation.
  - Use an advanced-generation cephalosporin, such as
    - Ceftriaxone (100 mg/kg/d, divided into 12-hour doses or given once daily).
    - Regimen is appropriate for immunized and non-immunized children.

- Lumbar puncture should be performed unless the clinical picture precludes meningitis.
  - If cerebrospinal fluid pleocytosis is present, add
    - Vancomycin (60 mg/kg/d divided into doses every 6 hours) *or*
    - A 10-day course of oral antimicrobial therapy is prescribed.

Preseptal (Periorbital) Cellulitis Caused by Inflammatory Edema of Sinusitis

- Antibiotic therapy (amoxicillin-clavulanate at 90 mg/kg/d in 2 divided doses) can be given orally if, at the time of the first examination
  - Eyelid swelling is modest *and*
  - The child does not look toxic *and*
  - The parents will adhere to management.
  - Otherwise, admission to the hospital and parenteral treatment should be undertaken.
- The only source of bacteriologic information is that obtainable by maxillary sinus aspiration.
  - Usually not performed
- Appropriate agents for outpatient therapy have activity against β-lactamase–producing organisms.
  - Amoxicillin-potassium clavulanate
  - Cefuroxime axetil
  - Cefpodoxime proxetil
- Parenteral agents include
  - Ceftriaxone.
  - Ampicillin-sulbactam.
    - This combination is an attractive choice.
    - Not approved for children <12 years.
  - After several days, once the affected eye has returned to near normal, a 10- to 14-day course of an oral antimicrobial agent is substituted.
- The use of topically applied intranasal decongestants (eg, oxymetazoline) has not been systematically evaluated.
  - Such agents may be helpful during the first 48 hours.

Orbital Infections

Antimicrobial Therapy

- Usually, patients with these symptoms are managed successfully with antimicrobial therapy alone.
- Empirical antimicrobial therapy should be chosen to provide activity against
  - *S aureus and*
  - *Streptococcus pyogenes and*
  - *Streptococcus anginosus and*
  - Anaerobic bacteria of the upper respiratory tract
    - Anaerobic cocci
    - *Bacteroides* species
    - *Prevotella* species
    - *Fusobacterium* species
    - *Veillonella* species
  - In addition to the usual pathogens associated with acute sinusitis
    - *S pneumoniae*
    - *H influenzae*
    - *Moraxella catarrhalis*
- Appropriate selections include
  - Ceftriaxone (100 mg/kg/d given as a single daily dose) *or*
  - Ampicillin-sulbactam (200 mg/kg/d divided into doses every 6 hours) plus vancomycin.
  - Immunocompromised children or those with diabetes are at higher risk of fungal orbital cellulitis.
- If surgery is performed
  - Gram stain of material drained from the sinuses or the abscess guides consideration of additional drugs or a change to the regimen.
  - When final results of culture are available, antibiotic therapy may be changed, if appropriate.
  - IV therapy is maintained until the infected eye appears nearly normal.
    - At that time, 2 weeks of oral antibiotic therapy can be substituted.

Surgical Drainage

- Presence of a large, well-defined abscess with complete ophthalmoplegia or impairment of vision prompts operative drainage of the paranasal sinuses and the abscess.
- Several studies have reported successful drainage of subperiosteal abscess via endoscopy.
  - Performed through an intranasal approach.
    - Avoids external incision
  - In many cases, a well-defined abscess is not seen.
  - Instead, inflammatory tissue is interposed between the
    - Lateral border of ethmoid sinus *and*
    - Swollen medial rectus muscle

WHEN TO ADMIT

- Hospitalize a child with a swollen eye
  - For parenteral therapy when bacteremic periorbital cellulitis is diagnosed

- For parenteral therapy when diagnosis of likely bacterial cellulitis is made and
  - Oral therapy has failed *or*
  - The child is febrile *or*
  - The child is <5 years.
- For parenteral therapy and consultation with an ophthalmologist when diagnosis is dacryocystitis
- When oral therapy has failed
- If eye is swollen shut and parenteral antibiotics and close observation are required for the management of inflammatory edema (sympathetic effusion)
- If proptosis, impairment of extraocular movements, diminished pupil reaction, or loss of visual acuity occurs
  - These signs herald subperiosteal abscess, orbital abscess, orbital cellulitis, and cavernous sinus thrombosis.
  - Presence indicates the need for parenteral antibiotics and the likely need for surgical intervention.

WHEN TO REFER

- Refer a child with a swollen eye to an ophthalmologist in the following instances:
  - When visual acuity is lost.
  - When any eyelid swelling occurs in an immunocompromised child or a child with diabetes, referral should be immediate.
    - The situation may require urgent treatment.
  - If conjunctivitis is diagnosed, referral is appropriate if clinical findings do not begin to improve after 5 days.
    - Circumstance suggests a diagnosis of adenovirus or herpes simplex infection.
  - When a chalazion is large and causes local irritation, incision and drainage of the chalazion may be required.
  - When dacryoadenitis has not begun to resolve after 5 days.
  - All patients with suspected or proven orbital cellulitis.

COMPLICATIONS

- Preseptal (periorbital) cellulitis caused by inflammatory edema of sinusitis
  - Inflammatory edema is part of a continuum.
  - More serious complications result from spread of infection outside the paranasal sinuses into the orbit.
  - Rarely, infection progresses despite initial optimal management of sympathetic effusions.

BACKGROUND

Risk Factors for Heart Disease and Atherosclerosis

- Multiple factors should be considered when assessing a child's global risk for premature cardiovascular disease.
  - For more on general aspects of screening, see Hypertension and Congenital and Acquired Heart Disease.
- This topic addresses 3 items that should be a part of routine pediatric preventive cardiology assessment for all children and adolescents.
  - Atherosclerosis
  - Obesity
  - Smoking
- Epidemiologic evidence indicates that atherosclerosis is not an inevitable consequence of aging.
  - It is an acquired disease with well-described risk factors.
  - Evidence of emerging risk factors in children.
- Atherosclerosis continues to be a leading cause of death and disability in the United States.
- The known risk factors for atherosclerosis include
  - Hypertension
  - Smoking
  - Elevated low-density lipoprotein cholesterol (LDL-C) level
  - Decreased high-density lipoprotein cholesterol (HDL-C) level
  - Diabetes mellitus
  - Advancing age
  - Male sex
  - A family history of premature heart disease
  - Hypertriglyceridemia
  - Sedentary lifestyle
  - Obesity

Hypercholesterolemia

- Hypercholesterolemia is a primary target in the prevention of atherosclerosis.
- Total cholesterol measures the cholesterol contained in several lipid particles, including
  - LDL-C, one of the atherogenic lipoproteins; the focus of screening algorithms
  - HDL-C, considered protective against the development of coronary heart disease
  - Very-low-density lipoprotein cholesterol
- Genetic and environmental factors play a role in the development of hypercholesterolemia.
  - Plasma cholesterol levels are influenced by the quantity and quality of dietary fat intake and the individual's ability to synthesize and degrade cholesterol.
  - Severe or familial hypercholesterolemia secondary to a defect in the LDL receptor occurs in ~1 in 500 individuals.
  - Children with this defect commonly have LDL-C values between 200 and 300 mg/dL.
    - This is 2–3 times higher than the acceptable limits of normal.
    - These children inherit the receptor defect and have a strong predilection for atherosclerotic heart disease as young adults.
  - >600 different mutations of the LDL receptor have been described.
    - ~50% of men with one of these mutations will have myocardial infarction by age 50 years.
    - 75%–85% will have myocardial infarction by age 60 years.
- Causes of secondary hypercholesterolemia include[1]
  - Exogenous
    - Drugs
      - Corticosteroids
      - Isotretinoin (Accutane)
      - Thiazides
      - Anticonvulsants
      - β-Blockers
      - Anabolic steroids
      - Certain oral contraceptives
    - Alcohol
    - Obesity
  - Endocrine and metabolic
    - Hypothyroidism
    - Diabetes mellitus
    - Lipodystrophy
    - Pregnancy
    - Idiopathic hypercalcemia
  - Storage diseases
    - Glycogen storage diseases
    - Sphingolipidoses
  - Obstructive liver diseases
    - Biliary atresia
    - Biliary cirrhosis
    - Alagille syndrome
  - Chronic renal diseases
    - Nephrotic syndrome

- Others
  - Anorexia nervosa
  - Progeria
  - Collagen disease
  - Klinefelter syndrome

Obesity and Physical Activity

- Obesity increases the risk for heart disease through its association with abnormalities, such as
  - Dyslipidemia
  - Hypertension
  - Insulin resistance
  - Glucose intolerance
  - Other undefined mechanisms
- The magnitude of the effect of childhood obesity on cardiac risk is not precisely known.
  - The US Preventive Services Task Force concluded that evidence was insufficient to recommend for or against screening of overweight children and adolescents.
  - Body mass index (BMI) and thickness of subcutaneous fat as measured by a skinfold test are correlated with the degree of coronary atherosclerosis in young adults.
- Adiposity in childhood is strongly associated with adiposity in adulthood.
- BMI percentiles are considered an appropriate measure of obesity.

Smoking

- The evidence that cigarette smoking is a risk factor for cardiovascular disease is overwhelming.
- Studies as early as 1940 documented a relationship between tobacco use and coronary artery disease.
- Tobacco use adversely affects lipid levels and is associated with
  - Decreased exercise capacity
  - Increased platelet aggregation
  - Increased incidence of respiratory illness
  - Increased incidence of low birth weight deliveries
  - Increased infant mortality
- Passive smoking is linked with changes in risk factors for coronary artery disease in children.
  - Associated with reduced HDL-C in nonsmoking children, as well as those with high-risk lipid profiles.
  - In 2006 the US Surgeon General issued an update on findings and recommendations to eliminate secondhand or passive smoke exposure for children.
- Adolescents are more likely than any other age group to smoke or use tobacco.
  - In 2011–2015 the National Youth Tobacco Surveys estimated that
    - In 2015, 1 in 4 high school students and 1 in 13 middle school students reported use of any tobacco product.
    - There were significant increases in the use of e-cigarettes and hookahs among middle and high school students
    - Use of conventional tobacco products, such as cigarettes and cigars, decreased, resulting in no change in overall tobacco product use.
    - e-Cigarettes were the most commonly used tobacco products in middle school and high school students.
- Children whose parents or siblings smoke are at an increased risk of beginning to smoke.
- Other factors that may predict smoking include
  - Peer influence
  - Less-educated parents
  - Independence and rebelliousness
  - Decreased concerns about the health risks associated with smoking
- Identifying these factors and addressing them openly is helpful in counseling.

GOALS

- Identify and treat potential atherosclerotic cardiac risk factors in children.
- Providers can educate children and families on preventive strategies.
- A goal of primary care is to prevent disease and development of risk factors in children.
  - The long-term hope is that early interventions will ultimately decrease the burden of atherosclerotic heart disease in adult life.
- The relatively new concept of primordial prevention challenges health care professionals to work to prevent risk factors.
  - Address the social and environmental factors that maintain them.
  - It is particularly important to address
    - Obesity
      - Smoking
      - Sedentary lifestyle

GENERAL APPROACH

Guidelines

- Optimal methods of heart disease prevention have generated controversy on such fundamental issues as
  - What age to begin screening
  - Who should be screened
  - How to treat individuals with elevated cholesterol levels
- The most recent report by the US Preventive Services Task Force found good evidence that children with dyslipidemia become adults with dyslipidemia.
  - The study concluded that the evidence was insufficient to recommend for or against screening of lipid disorders in children and adolescents.
- The pediatric National Cholesterol Education Program (NCEP) guidelines will undoubtedly be revised, as have the adult guidelines.
- A revision by the American Academy of Pediatrics (AAP) in 2008 has suggested lowering the treatment age to 8 years and adding 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase inhibitors, specifically pravastatin, to the arsenal of medications.
  - This change has not been endorsed by the NCEP or American Heart Association (AHA).
  - Controversy surrounds the lack of long-term data and potential effect of 40–50 years of exposure.
- For now, pediatricians should use the basic strategy proposed by the NCEP and endorsed by the AAP and AHA.

Risk Factors and Screening

- Although many risk factors for heart disease remain beyond the control of the individual, some can be modified.
  - Hyperlipidemia
  - Level of physical activity
- At least one factor—smoking—is completely avoidable.
- Several risk factors for coronary heart disease are now easily identified during childhood.
- The process of atherosclerosis and the habits that influence the risk of heart disease begin early in life.
- Scientifically based recommendations to begin prevention in childhood have been developed.
- Schedule for integrated cardiovascular health promotion in children.
  - 0–2 years
    - Family history
      - Early heart disease (≤55 years)
    - Cholesterol
      - Parent's total cholesterol ≥240 mg/dL
    - Obesity
      - Plot height and weight on growth charts.
      - Parental obesity present.
    - Blood pressure (BP)
      - Family history of hypertension
    - Diet
      - Diet history.
      - Early foods influence future food preferences.
    - Physical activity
      - Parent physical activity.
      - Discourage television and video viewing.
    - Smoking
      - Parental or household smoking?
      - If yes, counsel to quit and refer to smoking cessation.
  - 2–6 years
    - Family history
      - Update family history
      - Early heart disease (≤55 years)
      - Parent's total cholesterol ≥240 mg/dL
    - Cholesterol
      - Fasting lipids screening
      - Total cholesterol screening
    - Obesity
      - Plot height, weight, and BMI (kg/m^2) on growth charts.
      - BMI percentiles.
    - BP
      - Start routine BP measurement at 3 years of age (determine if >90th or 95th percentile for sex, age, and height).
    - Diet
      - Diet history
      - Low saturated fat diet including 1% or nonfat milk
      - Moderate salt intake
    - Physical activity
      - Encourage active child-parent play.
      - Limit sedentary behaviors, such as television and video viewing.
    - Smoking
      - Parental or household smoking?
      - If yes, counsel to quit and refer to smoking cessation.

- Antismoking counseling.
  - Includes immediate physical, social, and physiological effects of smoking; risk of addiction; counterarguing techniques; and resisting social and environmental pressures to smoke

- 6–10 years
  - Family history
    - Update family history.
    - Early heart disease (≤55 years).
    - Parent's total cholesterol ≥240 mg/dL.
  - Cholesterol
    - Fasting lipids screening
    - Total cholesterol screening
  - Obesity
    - Plot height, weight, and BMI (kg/m^2) on growth charts.
    - BMI percentiles.
  - BP
    - BP measurement
    - BP percentiles
  - Diet
    - Diet history
    - Low saturated fat diet including 1% or nonfat milk
    - Moderate salt intake
  - Physical activity
    - Physical activity history.
    - Lifestyle and family activities.
    - Limit sedentary behaviors, such as television and video viewing.
  - Smoking
    - Parental/household smoking?
    - If yes, counsel to quit; referral to smoking cessation.
    - Antismoking counseling.
      - Includes immediate physical, social, and physiological effects of smoking; risk of addiction; counterarguing techniques; and resisting social and environmental pressures to smoke

- >10 years
  - Family history
    - Update family history.
    - Early heart disease (≤55 years).
    - Parent's total cholesterol ≥240 mg/dL.
  - Cholesterol
    - Fasting lipids screening
    - Total cholesterol screening
  - Obesity
    - Plot height, weight, and BMI (kg/m^2) on growth charts.
    - BMI percentiles.
  - BP
    - BP measurement
    - BP percentiles
  - Diet
    - Diet history
    - Low saturated fat diet including 1% or nonfat milk
    - Moderate salt intake
  - Physical activity
    - Physical activity history.
    - Lifestyle and family activities.
    - Daily moderate to vigorous activity.
    - Limit sedentary behaviors.
  - Smoking
    - Parental or household smoking?
    - Assess child smoking.
    - If yes for either, counsel to quit and refer to smoking cessation.
    - Antismoking counseling.
      - Includes immediate physical, social, and physiological effects of smoking; risk of addiction; counterarguing techniques; and resisting social and environmental pressures to smoke
    - The risks of smoking should be a part of routine preventive care discussions.

SPECIFIC INTERVENTIONS

NCEP Recommendations

- The NCEP suggests 2 separate approaches to managing hypercholesterolemia in children.
  - Broad, population-based approach
  - Individualized patient approach
- Universal screening of all children is not recommended.

Population-Based Approach

- The panel suggests that all children >2 years follow the Step 1 diet.
  - ≤30% of total calories should come from fat.
  - <10% of total calories should come from saturated fat.
  - Total cholesterol consumption should be <300 mg per day.
  - The diet should contain a variety of foods.
  - The diet should be adequate to support growth and maintain ideal body weight for height and age.

- Characteristics of the AHA Step 1 and Step 2 diets include
  - Calories: Step 1 + 2: adequate for normal growth
  - Total fat: Step 1 + 2: ≤30% of calories
  - Saturated fat
    - Step 1: <10% of calories
    - Step 2: ≤7% of calories
  - Polyunsaturated fat: Step 1 + 2: ≤10% of calories
  - Monounsaturated fat: Step 1 + 2: remainder of fat calories
  - Carbohydrates: Step 1 + 2: ~55% of calories
  - Protein: Step 1 + 2: ~15%–20% of calories
  - Cholesterol
    - Step 1: <300 mg/dL per day
    - Step 2: <200 mg/dL per day

Individualized Screening

- In addition to the population-wide diet recommendations, the NCEP guidelines suggest
  - Assessing risk and performing cholesterol testing in children
    - >2 years with a positive family history
    - Who have a parent with hypercholesterolemia (total cholesterol ≥240 mg/dL)
    - Whose parent or grandparent has or had premature coronary heart disease (ie, onset of disease <56 years)
- Conditions that suggest heart disease include
  - A history of documented myocardial infarction
  - Angina pectoris
  - Peripheral vascular disease
  - Cerebrovascular disease
  - Sudden cardiac death
  - Coronary atherosclerosis as determined by angiography
  - A history of balloon angioplasty or coronary artery bypass graft surgery
- Children whose parental history is unknown or unobtainable may be screened to identify those in need of nutritional advice, especially if they have other risk factors.
- Parents with unknown cholesterol levels should be encouraged to obtain a full lipoprotein analysis.
- Cholesterol levels may need to be determined for children at higher risk independent of family history.
  - Those who smoke
  - Those who are obese
  - Those with diets rich in saturated fats and cholesterol
  - Those with diabetes mellitus
- For children with a family history of premature heart disease, guidelines suggest obtaining a fasting lipid profile that includes
  - Total cholesterol
  - LDL-C
  - HDL-C
  - Triglycerides
- Initial screening for children with a family history of hypercholesterolemia and no history of early heart disease should be done by measuring total cholesterol only.

Risk Stratification and Treatment

- The AHA and AAP recently proposed a risk stratification and treatment algorithm for children at increased risk for premature coronary heart disease.
- Children identified as needing special consideration for more careful attention to cardiovascular risk factors.
  - Homozygous or heterozygous familial hypercholesterolemia
  - Diabetes mellitus (type 1 or 2)
  - Chronic kidney disease or end-stage renal disease
  - Kawasaki disease
  - Congenital heart disease
  - Chronic inflammatory disease
  - Post–cardiac transplantation
  - Cancer treatment survivors

High-risk Stratification

- Tier I: high risk
  - Rationale: Exhibit coronary artery disease at <30 years: clinical or pathologic evidence
    - Disease process or condition
      - Homozygous familial hypercholesterolemia
      - Type 1 diabetes mellitus
      - Chronic kidney disease or end-stage renal disease
      - Post-orthotopic heart transplantation
      - Kawasaki disease with current coronary aneurysms
- Tier II: moderate risk
  - Rationale: accelerated atherosclerosis: pathophysiologic evidence
  - Disease process or condition
    - Heterozygous familial hypercholesterolemia
    - Kawasaki disease with regressed coronary aneurysms
    - Type 2 diabetes mellitus
    - Chronic inflammatory disease

- Tier III: at risk
  - Rationale: high-risk setting for accelerated atherosclerosis: epidemiologic evidence
  - Disease process or condition
    - Cancer treatment survivors
    - Congenital heart disease
    - Kawasaki disease without detected coronary aneurysms

Algorithm for Screening, With Tier-Specific Test Value Cutoffs

- High-risk pediatric populations
  - Step 1: risk stratification by disease process.
  - Step 2: Assess all cardiovascular risk factors.
    - If ≥2 comorbidities exist, assign the patient to the next higher risk tier for subsequent management.
  - Step 3: Define tier-specific intervention cutoff points or treatment goals.
  - Step 4: initial therapy.
    - Tier I: Initial management is therapeutic lifestyle change plus disease-specific management.
    - Tiers II and III: Initial management is therapeutic lifestyle change.
  - Step 5
    - Tiers II and III: If goals are not met after initial management, consider medication.

Tiers I, II, and III Treatment Recommendations[2]

- Growth and diet
  - Nutritionist evaluation and diet education for all; see Step 1 diet recommendations
  - Calculate BMI percentile for sex and height.
    - Step 1, if initial BMI >95th percentile
      - Age-appropriate reduced-calorie training for child and family.
      - Specific diet and weight follow-up every 2–4 weeks for 6 months; repeat BMI calculation at 6 months.
      - Activity counseling.
    - Step 2, if follow-up BMI is
      - >85th percentile for tier I *or*
      - >90th percentile for tier II *or*
      - >95th percentile for tier III
      - Weight-loss program referral plus exercise training program appropriate for cardiac status
- BP (tiers I, II, and III)
  - BP measurement or interpretation for age, sex, and height
    - Step 1, if systolic BP or diastolic BP is
      - Between the 90th and 95th percentiles *or*
      - >120/80 mm Hg on 3 separate occasions within 1 month.
      - Recommend decreased calorie intake, increased activity for 6 months.
    - Step 2, if initial systolic BP or diastolic BP is
      - >95th percentile (confirmed within 1 week) *or*
      - 6-month follow-up systolic BP or diastolic BP is >95th percentile.
      - Initiate pharmacologic therapy per Fourth Task Force recommendations.
- Lipids
  - Step 1, if initial LDL-C level ≥130 mg/dL (tier II) or >160 mg/dL (tier III)
    - Nutritionist training for Step 2 diet along with avoidance of trans fats for 6 months
  - Step 2, if repeat LDL-C level ≥130 mg/dL in tier II or >160 mg/dL in tier III and the child is 10 years of age
    - Initiate statin therapy with LDL-C goal of 130 mg/dL.
- Triglycerides
  - Step 1, if initial triglyceride level is between 150 and 400 mg/dL
    - Nutritionist training for low simple carbohydrate, low-fat diet.
    - If elevated triglycerides are associated with excess weight, refer to a nutritionist for weight loss management: energy balance training plus activity recommendations.
  - Step 2, if triglyceride level is between 700 and 1,000 mg/dL, initial or follow-up
    - Consider fibrate or niacin if the child is >10 years.
    - Weight loss is recommended when triglyceride elevation is associated with overweight or obesity.
- Glucose (tiers I, II, and III, except for patients with diabetes mellitus)
  - Step 1, if fasting glucose level is between 100 and 126 mg/dL.
    - Recommend a reduced-calorie diet and increased activity aimed at 5%–10% decrease in weight over 6 months.

- Step 2, if repeat fasting glucose level is between 100 and 126 mg/dL.
  - Recommend insulin-sensitizing medication as per an endocrinologist.
- If the casual glucose is >200 mg/dL or fasting glucose level is >126 mg/dL, diabetes mellitus can be diagnosed.
  - Endocrine referral for evaluation and management
- Maintain hemoglobin (Hb) A_{1c} at <7%.

■ Smoking (tiers I, II, and III)
- Step 1: Obtain parental smoking history at every visit and child smoking history beginning at age 10 years. Provide active antismoking counseling for all; a smoke-free home is strongly recommended at each encounter.
- Step 2: Provide smoking cessation referral for any history of cigarette smoking.

■ Activity (tiers I, II, and III)
- For children in all tiers, participation in activity is at the discretion of the physician.
- For specific cardiac diagnoses, such as Kawasaki disease and congenital heart disease, activity guidelines are referenced.
  - Step 1: Obtain specific activity history for each child, focusing on time spent in active play and screen time (television + computer + video games); goal is
    - ≥1 hours of active play per day.
    - Screen time limited to ≤2 hours per day.
    - Encourage activity at every encounter.
  - Step 2: If goals are not met after 6 months, consider referral for exercise testing and recommendations from an exercise specialist.

Tier I–Specific Treatment Recommendations[2]

■ Rigorous age-appropriate education in diet, activity, and smoking cessation for all.
- Specific therapy as needed to achieve BP, LDL-C, glucose, and HbA_{1c} goals as indicated for each tier
  - Timing should be individualized for each patient and diagnosis.
- Homozygous familial hypercholesterolemia
  - LDL management: scheduled apheresis every 1–2 weeks beginning at diagnosis to maximally lower LDL-C, plus statin and cholesterol absorption inhibitor.
  - Treatment per cardiologist or lipid specialist; specific therapeutic goals for LDL-C are not meaningful with this diagnosis.
  - Assess BMI, BP, and fasting glucose: Step 1 management for 6 months.
  - If tier I goals are not achieved, proceed to Step 2.
- Type 1 diabetes mellitus
  - Intensive glucose management per an endocrinologist, with frequent glucose monitoring or insulin titration to maintain plasma glucose level <200 mg/dL and HbA_{1c} <7%.
  - Assess BMI and fasting lipids: Step 1 management of weight, lipids for 6 months.
  - If goals are not achieved, proceed to Step 2; statin therapy if >10 years to achieve tier I treatment goals.
  - Initial BP >90th percentile: Step 1 management plus no added salt, increased activity for 6 months.
  - BP consistently >95th percentile for age, sex, and height: Initiate angiotensin-converting enzyme inhibitor therapy with BP goal to be <90th percentile or <130/80 mm Hg, whichever is lower.
- Chronic kidney disease or end-stage renal disease
  - Optimization of renal failure management with dialysis or transplantation as per nephrologist.
  - Assess BMI, BP, lipids, and fasting glucose: Step 1 management for 6 months.
  - If goals are not achieved, proceed to Step 2; statin treatment if >10 years to achieve tier I treatment goals.
- After heart transplantation
  - Optimization of antirejection therapy, treatment for cytomegalovirus, routine evaluation by angiography or perfusion imaging per transplant physician.
  - Assess BMI, BP, lipids, and fasting glucose: Initiate Step 2 therapy immediately, including statins, in all patients >1 year to achieve tier I treatment goals.
- Kawasaki disease with coronary aneurysms
  - Antithrombotic therapy, activity restriction, ongoing myocardial perfusion evaluation as per cardiologist.
  - Assess BMI, BP, lipids, and fasting glucose: Step 1 management for 6 months.
  - If goals are not achieved, proceed to Step 2; statin treatment if >10 years to achieve tier I treatment goals.

- Most of the information on the risk of heart disease in adults is based on fasting LDL-C values.
  - Recommendations in children are also based on fasting LDL-C values.
  - Treatment values are based on percentile ranks of children in the United States that exceed the upper norms.
    - Values >95th percentile for children are considered *high*.
      - Total cholesterol level >200 mg/dL and LDL-C >130 mg/dL
    - Values <75th percentile are considered *acceptable*.
      - Total cholesterol level <170 mg/dL and LDL-C <110 mg/dL
    - Values between these limits are considered *borderline*.
  - A lipid profile, including an assessment of LDL-C, should be ordered if
    - Initial fasting total cholesterol level is high.
    - After an initial borderline value, the average of the first and second test values is >170 mg/dL.
  - The final evaluation should be based on the average of at least 2 LDL-C measurements.
    - Treatment should follow the general strategy described.
    - Individualized approach: algorithm for assessing and managing hyperlipidemia based on LDL cholesterol.
      - Acceptable (LDL-C <110 mg/dL): Repeat cholesterol testing in 5 years, and advise the family to follow the Step 1 diet.
      - Borderline (LDL-C 110–129 mg/dL): Advise the family to follow the Step 1 diet, provide advice on other risk factors, and reevaluate the child in 1 year.
      - High (LDL-C ≥130 mg/dL): Before recommending dietary or medical treatment, obtain a history detailing the use of drugs, such as isotretinoin (Accutane), steroids, and alcohol, to identify any secondary cause of hypercholesterolemia. In addition, screen for other secondary causes of elevated cholesterol, such as liver, thyroid, and renal disease.
- The initial dietary treatment is to follow a Step 1 diet.
  - This diet is safe and efficacious for managing children with borderline to high LDL-C levels.
  - The child must consume adequate calories while decreasing fat intake.
  - Current dietary guidelines suggest that all children should consume enough calories to reach or maintain desirable weight.
  - Weight reduction in overweight and obese children is often helpful in correcting cholesterol profiles.
  - In contrast with adults, some children with hypercholesterolemia are not overweight.
    - In children who are not overweight, caloric restriction is not the primary treatment for hypercholesterolemia.
  - For children whose LDL-C level remains >130 mg/dL after at least 3 months of careful adherence to the Step 1 diet, the Step 2 diet is advised.
    - No more than ~30% of calories from total fat (similar to the Step 1 diet)
    - <7% of calories (compared with 10% in the Step 1 diet) from saturated fat
  - Adherence to the Step 2 diet is often improved by having the family meet with a registered dietitian trained in managing hyperlipidemia in children.
  - For children >10 years whose LDL-C level remains >190 mg/dL after 6–12 months of dietary therapy
    - Consider drug treatment with bile acid–binding resins.
      - Cholestyramine
      - Colestipol
    - Drug therapy should also be considered for those who maintain an LDL-C level >160 mg/dL and have a family history of premature cardiovascular disease.
  - Dietary products are available in supermarkets.
    - Special margarines with plant sterols and stanols to reduce LDL-C absorption.
    - The 2005 AHA/AAP dietary recommendations caution against using these spreads.
      - Given the possible decrease in absorption of fat-soluble vitamins and β-carotene
  - Other medications, such as HMG CoA-reductase inhibitors (or statins), are not recommended routinely for children.
    - Except in consultation with a lipid specialist.
    - For children in designated high-risk groups (see previous definition) who are nonresponsive to diet/exercise intervention.
    - A revision by the AAP in 2008 suggested lowering the treatment age to 8 years and adding statins, specifically pravastatin, to the arsenal of medications.

- This change has not been endorsed by the NCEP or AHA.
- Controversy surrounds the lack of long-term data and potential effect of 40–50 years of exposure.

- The cholesterol screening and dietary treatment guidelines can be initiated safely by a primary care practitioner interested in nutrition and prevention of heart disease.
  - Initiation includes
    - A review of family history.
    - Evaluation for secondary causes of hyperlipidemia.
    - Dietary counseling.
    - Identification of children with risk factors for coronary heart disease should lead to screening of other family members.
      - Many risk factors tend to cluster in families.
  - Evaluation by a lipid specialist with continued general support from the primary care pediatrician is recommended.
    - When the child has severe hypercholesterolemia that is
      - Unresponsive to dietary treatment
      - From a family with early onset of heart disease

Obesity and Physical Activity

- A common and reasonable approach in defining obesity in children is based on the use of age and sex percentiles of BMI.
  - BMI = kg/m^2, where body weight is measured in kilograms and height is measured in meters.
  - Children with a BMI >95th percentile are considered *obese*.
  - Those with a BMI between the 85th and 95th percentile are considered *overweight*.
  - In 2000, the Centers for Disease Control and Prevention (CDC) adopted different terms to avoid negative labeling of children.
    - *Risk of overweight* is used for children between the 85th and 95th percentile.
    - *Overweight* is used for those >95th percentile.
- Current recommendations from the AHA and AAP suggest that
  - Pediatricians should feel confident in assessing and charting BMI, beginning at 2 years of age.
  - Pediatricians should counsel parents to address the at-risk child's eating and activity patterns.
- BMI and percentiles can be easily calculated and charted for all children.
  - Charting materials for BMI by age and sex should be a part of every primary care pediatrician's practice.
  - Free materials (growth charts) from the CDC can be found online.
- Overweight children (BMI >95th percentile) should be further screened for
  - Hypertension
  - Orthopedic symptoms
  - Hypoventilation
  - Abnormalities of lipids and glucose metabolism
- The magnitude of the abnormalities is an important consideration; additional specialty evaluations should be recommended in individual situations.
- No single treatment program for overweight children has been proved to be uniformly successful.
- A combination of diet and exercise therapy with behavioral modification and family counseling is often needed and is the first-line approach.
- AHA pediatric dietary strategies for individuals >2 years.[3]
  - Balance dietary calories with physical activity to maintain normal growth.
  - Perform 60 minutes of moderate to vigorous play or physical activity daily.
  - Eat vegetables and fruits daily; limit juice intake.
  - Use vegetable oils and soft margarines low in saturated fat and trans-fatty acids instead of butter or most other animal fats in the diet.
  - Eat whole-grain breads and cereals rather than refined grain products.
  - Reduce the intake of sugar-sweetened beverages and foods.
  - Use nonfat (skim) or low-fat milk and dairy products daily.
  - Eat more fish, especially oily fish, broiled or baked.
  - Reduce salt intake, including salt from processed foods.
- The importance of physical activity in preventing or ameliorating cardiac risk factors (obesity, hyperlipidemia, hypertension) has been increasingly recognized.
  - In adults, higher levels of physical activity have been associated with decreased rates of heart disease, above and beyond changes in known cardiac risk factors.

- Health care professionals should encourage children to make physical activity a part of their daily routine.
  - A Cochrane Review found that many diet and exercise interventions improve eating behaviors and physical activity levels but are not effective in preventing weight gain.
  - Studies also suggest that children are more likely to be physically active if their parents are active.

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Proteinuria

DEFINITION

- In adults, *proteinuria* is defined as a urinary protein excretion >150 mg/d.
- In children, *proteinuria* is defined as protein excretion >4 mg/m^2/h.
  - Finding proteinuria in a single urine specimen in children and adolescents is relatively common.
  - Persistent proteinuria is called *fixed proteinuria.*

HISTORY

- First steps in evaluating a child with proteinuria
  - Thorough history
  - Physical examination, looking for indicators of renal disease
- Basic evaluation of proteinuria
  - Presence or absence of symptoms
  - Amount of protein loss
  - Presence or absence of associated findings, such as
    - Hematuria
    - Hypertension
    - Azotemia
  - Other urinary or systemic abnormalities
- Warning signs of proteinuria
  - Persistent, fixed, non-orthostatic proteinuria
  - Proteinuria associated with other urinary abnormalities, such as hematuria, or urinary casts
  - Proteinuria associated with renal insufficiency, anemia, or hypertension
  - Family history of renal disease, kidney stones, dialysis, deafness, or autoimmune conditions
  - Proteinuria associated with comorbidities such as
    - Preterm birth
    - Congenital anomalies of other organ systems
    - Hypertension
    - Diabetes
    - Obesity
- Postural or orthostatic proteinuria
  - Children with this type usually are asymptomatic.
    - Proteinuria usually is found on a routine urinalysis.
    - When upright, they may spill abnormal amounts of protein in the urine.
    - When supine, they have normal urinary protein excretion.
      - After they are recumbent for a few hours (asleep overnight), proteinuria decreases to normal range or disappears.
- Transient proteinuria
  - Can accompany
    - Fever
    - Exercise
    - Stress
    - Dehydration
    - Congestive heart failure
    - Seizures
  - Usually does not exceed 2+ on the dipstick test
- Symptomatic proteinuria
  - Patients with a combination of nephritis and nephrotic syndrome pose a clinical challenge even to the most experienced nephrologist.
  - History should include questions about
    - Recent illnesses
    - Fever
    - Rash
    - Arthralgias
    - Change in urine output and color
    - Symptoms of chronic disease
      - Weight loss
      - Fatigue
    - Duration and severity of symptoms
  - Pay attention to
    - History of urinary tract infections
    - Family history of
      - Urinary reflux
      - Hypertension
      - Deafness

PHYSICAL EXAMINATION

- Measurements of growth parameters, as well as documentation of the presence or absence of any joint or skin lesions
- Blood pressure
- Identification of edema, ascites, and pallor

DIFFERENTIAL DIAGNOSIS

Non-pathological Proteinuria

- Results from adjustment of the kidney to extraneous physiological conditions
  - Growth
  - Exercise
  - Fever
  - Systemic illness
- Level of proteinuria
  - Generally <1 g/d
  - Not associated with edema

- Postural or orthostatic proteinuria
  - Cause is unknown.
    - It has been postulated that it might result from higher than normal release of norepinephrine and angiotensin II on standing, or transient compression of the left renal vein in the fork between the superior mesenteric artery and the aorta (renal nutcracker).
  - No edema, hypertension, or hematuria.
  - Normal creatinine clearance and complements.
- Transient proteinuria
  - Proteinuria associated with vigorous exercise rarely exceeds 2+ on dipstick test.
  - Seems related to intensity rather than duration of exercise.
  - May be explained by
    - Increased glomerular filtration barrier permeability
    - Partial inhibition of tubular reabsorption of protein
  - Effect of exercise increases with age.
  - Considered benign if proteinuria resolves after 48 hours of rest.

Pathological Proteinuria

Persistent or Fixed Asymptomatic Proteinuria

- Can be classified as glomerular or tubular
  - Glomerular proteinuria is the more common of the 2 forms.
    - Associated with increased permeability of the glomerular filtration barrier
    - May be selective (plasma proteins with molecular weights up to and including albumin), as in minimal change disease
    - May be nonselective (albumin and large molecular weight proteins, eg, immunoglobulin G [IgG]), as in most forms of glomerulonephritis
  - Tubular proteinuria results from decreased tubular protein reabsorption caused by tubular dysfunction.
- Glomerular causes
  - Nephrotic syndrome
    - Idiopathic
    - Minimal change disease
    - Mesangial proliferation
    - Focal segmented glomerulosclerosis
    - Membranous nephropathy
  - Glomerulonephritis
    - Postinfectious
    - IgA nephropathy
    - Membranoproliferative glomerulonephritis
  - Systemic disease
  - Systemic lupus erythematosus
  - Vasculitis
  - Tumor
  - Subacute bacterial endocarditis
  - Infection (HIV, hepatitis)
  - Drugs or toxins
  - Obesity
  - Other
- Tubular causes
  - Genetic
    - Polycystic kidney disease
    - Cystinosis
    - Wilson disease
    - Lowe (oculocerebrorenal) syndrome
    - Galactosemia
    - Renal tubular acidosis
    - Dent disease
  - Acquired
    - Interstitial nephritis
    - Acute tubular necrosis
    - Heavy metal poisoning
    - Drugs or toxins

Symptomatic Proteinuria

- When defined as a nephrotic syndrome, often associated with
  - Gravity-dependent edema
  - Hypoalbuminemia
  - Hyperlipidemia
- Some children with nephrotic-range proteinuria and hypoalbuminemia remain completely asymptomatic.
- Edema in nephrotic syndrome results from several factors acting in concert, including
  - Increased distal nephron sodium reabsorption
  - Increased capillary permeability
  - Low plasma oncotic pressure associated with hypoalbuminemic states
- May be associated with other abnormalities, including
  - Hematuria
  - Hypertension
  - Azotemia, as seen in glomerulonephritis

LABORATORY EVALUATION

- Diagnosis of proteinuria depends on laboratory assessment of the level of protein in the urine.
  - Presence of persistent proteinuria on repeat testing indicates renal disease until proved otherwise.

- Presence of proteinuria should be confirmed by a urine protein to creatinine (P/Cr) ratio of >0.2 (>0.5 for children 6 months–2 years) on a first morning urine sample.
- Once confirmed, proteinuria should be quantified by a 24-hour urine collection for measurement of protein and creatinine to determine adequacy of the sample.

Dipstick Test

- Most commonly performed urine screening method for protein.
- Tetrabromophenol on the reagent strip reacts with the amino group of the protein and changes the color of the strip.
- Test reports findings as
  - Negative
  - Trace
  - 1+ (30 mg/dL)
  - 2+ (100 mg/dL)
  - 3+ (300 mg/dL)
  - 4+ (2,000 mg/dL)
- Primarily detects albumin.
- Less sensitive to low molecular weight proteins and γ-globulins.
- Result of ≥1+ in a specimen with a specific gravity of <1.015 indicates abnormal protein loss.
- False-negative results may be caused by highly dilute urine.
- False-positive results may be caused by
  - Concentrated urine
  - Extremely alkaline urine
  - Prolonged immersion of the strip
  - Hematuria, pyuria, or bacteriuria
  - Presence of detergents and contaminating antiseptics
    - Chlorhexidine
    - Benzalkonium chloride
  - Presence of antibiotics
    - Penicillins
    - Cephalosporins
    - Sulfonamides
    - Tolbutamide
  - Presence of radiographic contrast materials
- An alternative office procedure is precipitation with sulfosalicylic acid.
  - Provides a more accurate estimate of the total urinary proteins.
    - Includes those of low molecular weight
  - To prevent false-positive results, should be performed on the first urine voided in the morning.
  - Results should be confirmed by urinalysis.

Timed Urine Sample

- Traditional and most accurate method.
- Measures protein in a timed sample collected over a 24-hour period.
- Patient is instructed to void right after waking in the morning and discard this first urine.
- All subsequent urines are collected.
- Last sample added to the collection should be 24 hours after the first sample.
- In adults, a protein excretion of <150 mg in 24 hours is considered normal.
- In children, excretion rates are categorized as
  - Reference range: <4 mg/m^2/h
  - Abnormal: 4–40 mg/m^2/h
  - Nephrotic-range proteinuria: >40 mg/m^2/h
- Sample adequacy can be determined by measuring the creatinine excretion in the sample.
  - Steady-state daily creatinine excretion is
    - 20 mg/kg/d in children 1–12 years of age
    - 22–25 mg/kg/d in older children
- Weaknesses of this method
  - Cumbersome
  - Can be impractical in children
  - Frequent errors from under- and over-collection

Urine Protein to Creatinine Ratio

- Measurement of the P/Cr ratio in an untimed (spot) urine sample.
- Reliable for classification of proteinuria.
- Easier than 24-hour urine collection.
- Studies in adults and children have shown strong correlation between untimed urine P/Cr ratio and 24-hour urine collection.
  - Nephrotic-range proteinuria: ratio >3.5
  - Reference
    - Ratio <0.2 in patients ≥2 years
    - Ratio <0.5 in children aged 6–24 months

Postural or Orthostatic Proteinuria

- Children with asymptomatic proteinuria should be assessed.
- Collect a first-morning urine sample; if negative for protein on the dipstick, or if the measured P/Cr ratio is <0.2, a presumptive diagnosis of orthostatic proteinuria can be made.
- The more formal (but not currently used) orthostatic test for postural proteinuria includes 2 separate collections.
  - Supine position.
  - Upright position.
  - At bedtime, the child goes to bed without voiding.
  - 30 minutes later the child is asked to void.

- Urine is discarded and time is noted as the start of the collection in supine position.
- Child is then given a large glass of water or another fluid and allowed to sleep.
- All urine passed during the night, including the first specimen voided the next morning, is collected in a jar (specimen 1).
- Time of the first morning voiding is recorded.
- Child goes about daily activities.
- All urine is collected in a second jar (specimen 2) for approximately the next 12 hours.
- This collection is the upright collection and ends at bedtime, when time is again recorded.
- In patients with orthostatic proteinuria
  - Sample obtained in the supine position will be free of protein or will contain a typical amount of protein.
  - Sample obtained in upright position will contain an abnormal amount of protein.

- Children with orthostatic proteinuria generally excrete <1 g of protein in 24 hours.

Persistent or Fixed Asymptomatic Proteinuria

- Patients with a positive dipstick test result (≥1+) should undergo a more accurate test.
  - P/Cr ratio
  - Quantitative measurement of protein excretion
- Orthostatic proteinuria should be excluded by repeat measurements on a first morning void.
- In the absence of other abnormalities, patients are diagnosed as having *fixed proteinuria* with ≥2 positive semiquantitative or quantitative tests, 1–2 weeks apart.

Other Tests

- Level of kidney function can be determined by
  - Serum electrolytes
  - Blood urea nitrogen
  - Creatinine
- Determination of the severity of metabolic changes that occur as a result of urine protein loss guided by
  - Serum albumin
  - Cholesterol
  - Triglycerides
- Based on the child's history, the following testing may be indicated:
  - Complement levels
  - Anti–streptolysin O titers
  - Hepatitis serologic testing
  - HIV testing
- Children should be routinely screened by a standard dipstick test on 2 occasions.
  - Before starting school
  - In early adolescence
- Subsequent testing should be performed as needed.
- Assessment of total protein is appropriate in children to identify albuminuria and low molecular weight proteinuria.
  - Under most circumstances, spot urine samples should be used to detect and monitor proteinuria in children.
  - Obtaining 24-hour timed urine collections usually is unnecessary.
  - First morning specimens are preferred.
  - Random specimens are acceptable if a first morning sample is unavailable.
  - Patients with a positive dipstick test result of ≥1+ should undergo confirmation by assessment of the P/Cr ratio within 3 months.

IMAGING

- Renal ultrasound
  - Normal in postural or orthostatic proteinuria, but not usually performed in the evaluation process
  - Should be performed when structural abnormalities are a possibility

DIAGNOSTIC PROCEDURES

- Indications for renal biopsy
  - Fixed, asymptomatic, isolated proteinuria >1 g/d
  - Persistent proteinuria <1 g/d *plus*
    - Persistent hematuria and cellular casts
    - Renal insufficiency
    - Persistently low complement levels
    - Hypertension
    - Systemic symptoms, such as recurrent rashes, joint pains, or fever
    - Systemic lupus erythematosus
    - Family history of kidney disease or autoimmune disease
  - Corticosteroid-resistant nephrotic syndrome

TREATMENT APPROACH

- Medications that reduce proteinuria may provide important long-term benefits for patients with chronic kidney disease, and this beneficial effect has been extrapolated for children.

SPECIFIC TREATMENT

- Orthostatic proteinuria
  - Child should be monitored with annual office visits and check of urine P/Cr ratio.
- Isolated fixed proteinuria <1 g/d detected (urine P/Cr ratio <1:1)
  - Restrictions on the child's lifestyle and physical activity are not necessary.
  - Children with proteinuria should receive the recommended daily allowance of protein for their age.
  - Twice-yearly visits with determination of urine P/Cr ratio are sufficient.
  - Patient should be assessed for hematuria and hypertension.
  - If proteinuria persists for >1 year, renal biopsy should be considered.

WHEN TO REFER

- Patient should be referred to a pediatric nephrologist if any abnormalities are found during the initial workup.
- Other indicators include
  - Persistent, fixed, non-orthostatic proteinuria
  - Proteinuria associated with other urinary abnormalities, such as hematuria
  - Proteinuria associated with renal insufficiency, anemia, or hypertension
  - Family history of renal disease, deafness, or autoimmune condition
  - Proteinuria associated with comorbidities such as
    - Preterm birth
    - Congenital anomalies of other organ systems
    - Hypertension
    - Diabetes
    - Obesity

WHEN TO ADMIT

- Anasarca resistant to outpatient management
- Proteinuria associated with significant renal insufficiency
- Proteinuria associated with significant hypertension

FOLLOW-UP

- Postural or orthostatic proteinuria
  - Long-term follow-up studies in adults have documented the benign nature of orthostatic proteinuria.
  - Rare cases of glomerulosclerosis have been identified later in life in patients who initially were found to have proteinuria with an orthostatic component.
    - Long-term follow-up of children is necessary if the proteinuria does not resolve.
    - Signs to anticipate include
      - Appearance of hematuria
      - Hypertension
      - Increase in serum creatinine concentration
      - Proteinuria >1 g/d

COMPLICATIONS

- Proteinuria may indicate
  - Renal injury
  - Progressive renal disease
- Proteinuria is an established independent risk factor for cardiovascular disease.
  - Large losses of protein through the urine lead to hypercholesterolemia and hypertriglyceridemia.

DEFINITION

- Pruritus, or itch, is the subjective perception of a cutaneous disturbance that is relieved by scratching or rubbing.
- Usually not brought to the primary care physician's attention unless it is generalized, chronic, or associated with an eruption.
  - In such instances, pruritus must be treated with great respect.
    - Severe itching can be physically incapacitating.

HISTORY

- Most common cutaneous diseases associated with generalized pruritus can be diagnosed based on history and physical examination.
- Infestation.
  - Are any individual pruritic papules found with a central punctum?
  - Are they on exposed or nonexposed areas?
  - Does anyone else in the family have similar lesions?
- Atopic dermatitis.
  - Family history of allergy, asthma, or eczema in a child
  - Chronic eczematous dermatitis over
    - Extensor surfaces in infancy
    - Flexural areas in childhood
- Acute urticaria.
  - Exposure to a drug or other ingestant.
  - In 90% of cases, the cause of acute urticaria remains unknown.
- Contact allergic dermatitis or contact irritant dermatitis.
  - Environmental exposures
- Certain circumstances alter interpretation, eg, the itch threshold in and around areas of active dermatitis can be lowered with
  - Psychic stress.
  - Decreased skin hydration.
  - Increased skin temperature.
  - Nighttime.
  - Pain can inhibit the itch sensation, and scratching can stimulate pain receptors.

PHYSICAL EXAMINATION

- Infestation
  - Individual pruritic papules with central punctum
- Contact dermatitis
  - Recognizable because of a linear array of
    - Papulovesicular erythematous lesions
    - Sharp borders that conform to the shape of the contactant
- Acute urticaria
  - Produces intensely pruritic, erythematous, and edematous plaques and papules (wheals, hives).
  - Physical urticaria (brought on by a physical stimulus) is demonstrated by dermatographism.
- Miliaria (heat rash)
  - Pinpoint crystalline or erythematous papules in areas of occlusion and sweating

DIFFERENTIAL DIAGNOSIS

- In children, generalized pruritus is more commonly associated with local cutaneous disease than systemic disease.
- The major differential diagnoses of generalized pruritus with skin lesions in children are
  - Infestation
    - Scabies
    - Pediculosis
    - Insect bites
  - Atopic dermatitis
  - Miliaria crystallina and rubra (heat rash)
  - Contact dermatitis
  - Acute or chronic urticaria
- Children may itch with cutaneous diseases, such as
  - Psoriasis
  - Lichen planus
  - Linear immunoglobulin A bullous disease of childhood
- Systemic causes of itch in the child who has pruritus but no skin lesions are
  - Hyperthyroidism and hypothyroidism
  - Leukemia or lymphoma
  - Chronic renal failure
  - Obstructive biliary disease
  - Xerosis (generalized dry skin)

LABORATORY EVALUATION

- For the child who has pruritus with no primary skin disorder, assess for possible systemic causes.
  - Complete blood cell count with differential
  - Urinalysis
  - Complete chemistry panel, including liver function tests
  - Thyroid function tests (thyroid stimulating hormone and free thyroxine [T_4])
- With urticaria, if the patient has not used any new drug or food, and if the hives persist despite regular use of antihistamines for several days, rule out occult streptococcal, mycoplasmal, and viral infections by performing
  - Throat culture and a complete blood cell count with differential

- Screens for mycoplasmal disease and infectious mononucleosis

IMAGING

- Consider chest radiography for the child with pruritus and no primary skin disorder.

DIAGNOSTIC PROCEDURES

- Skin biopsy, in rare instances of undiagnosed but persistent lesions

TREATMENT APPROACH

- To relieve itching and prevent scarring (mental and physical), the scratch-itch cycle must be broken.
  - Itching provokes scratching.
  - When the scratching stops, the itching returns.
- To control itching, the following steps can be helpful:
  - Keep fingernails short to prevent damage from scratching.
  - Keep the child fully clothed except when applying medications.
  - Apply bland emollient creams frequently, especially after bathing.
    - Over-washing may dry out the skin and worsen itch, especially if occlusive cream is not used to seal water in the skin.
    - Home humidifiers may increase relative humidity and lessen dry skin itch.
  - Apply cool compresses to relieve intense pruritus and to remove crusts and debris.
  - Apply topical steroids for short periods (generally <2 weeks) to control inflammation.
  - Increase the dose of antihistamine until the scratching stops or marked drowsiness occurs.
    - Then reduce the dose to a level that controls scratching but does not cause drowsiness.
  - Advise the family to avoid stress, heat, and irritants (eg, pool, pet dander).
  - See the patient frequently to provide support.
  - If the child is old enough to understand, explain why these methods are being used.

SPECIFIC TREATMENT

Infestation

- Topical steroids
- Long clothes
- Repellents

Atopic Dermatitis

- Hydration and emollients are the mainstay of therapy.
- Mid- and low-potency topical steroids for inflammation.
- Antibiotics for secondary infection.
- Cool compresses to bring the scratch-itch cycle under control.
- Topical immunomodulators (tacrolimus and pimecrolimus).
  - Short courses (<8 weeks) may be helpful in relieving atopic itch on
    - Facial skin
    - Thin areas, such as the axillae
  - These medications should not be prescribed for long-term therapy.
- Antihistamine in a tolerable (non-soporific) dose may relieve itch.
  - Should be given ~1 hour before bedtime.
    - The itch threshold is lower at night.
  - Hydroxyzine seems to be the most effective agent.
  - Data about the use of nonsedating antihistamines for controlling itch are not consistent.

Heat Rash

- Controlled by simple measures, such as
  - Dusting powders
  - Avoidance of tight clothing
  - Reduced exposure to high ambient temperatures

Contact Dermatitis

- For use of antihistamines, topical steroids, and compresses, see Atopic Dermatitis section.

Topical Capsaicin, Menthol, Phenol, Doxepin, and Pramoxine

- May be indicated for localized use in some cases.
- Potential for contact irritation and systemic absorption limits prolonged or widespread use.

UV-B Light Therapy

- May be helpful for generalized pruritus, such as occurs in
  - Biliary cirrhosis
  - Severe chronic atopic dermatitis

Neurologic "Sensor Resetting"

- May be useful in chronic localized and intractable itch.
- Mirror treatment is used to fool the brain into believing the affected area is normal.

WHEN TO REFER

- Pruritus with uncommon disease (eg, psoriasis, bullae)
- Chronic pruritus without cutaneous disease (to evaluate for systemic cause)
- Pruritus uncontrolled by usual topical steroids and antihistamines

COMPLICATIONS

- A child with pruritus, whatever the cause, is at risk for
  - Psychological damage
  - Infection secondary to impetiginization
  - Scarification
- Scratching or rubbing can
  - Produce extensive disfigurement.
    - Linear excoriations
    - Lichenified plaques
  - Predispose the patient to cutaneous infections.
  - Cause social isolation.
    - The child may be viewed as being contagious or unclean.

DEFINITION

- Common chronic inflammatory dermatosis clinically characterized by well-demarcated, erythematous papules and plaques with overlying silvery-white scale
- *Plaque psoriasis*
  - Most common.
  - Scalp, elbows, knees, and lumbosacral regions are the most commonly affected areas, often with bilateral symmetry.
  - The scalp is the most frequently involved site in children.
  - Facial psoriatic lesions, especially around the eyes, are more common in affected children and may be the only involved site.
- *Guttate psoriasis*
  - Second most common
  - Small "drop-like" lesions with characteristic scale
  - More common in children than adults
  - May be triggered by group A streptococcal infections

SIGNS AND SYMPTOMS

- Plaque psoriasis
  - Large erythematous plaques with overlying silvery-white or grayish scale
    - Elbows
    - Knees
    - Scalp
    - Ears
    - Gluteal cleft
    - Umbilicus
- Guttate psoriasis
  - Can be the first manifestation of psoriasis
  - Characteristics of lesions
    - 2–10 mm
    - Widespread
    - Symmetrically distributed
    - Round or oval erythematous papules and plaques with silvery-white scale
    - Often have a predilection for the trunk and proximal extremities
- Inverse psoriasis
  - Glazed, bright-red erythema with minimal scale
    - Diaper area
    - Axillae
    - Inframammary
    - Groin
    - Postauricular area
- Pustular psoriasis
  - Widespread bright-red erythema studded with 1- to 2-mm pustules
  - Deep-seated 2- to 4-mm pustules in areas of erythema and scaling
  - Widespread, especially in
    - Flexural areas
    - Genitals
    - Finger web spaces
    - Palms
    - Soles
- Erythrodermic psoriasis
  - Bright-red erythema with massive exfoliation
  - Widespread
- Nail involvement psoriasis
  - May occur with or without skin involvement
  - Nail pitting (most characteristic finding)—multiple, small, irregularly spaced depressions in the nail plate
  - Other nail findings
    - Discoloration
    - Onycholysis (separation of the nail from the nail bed)
    - Longitudinal striations
    - Subungual hyperkeratosis
  - May be associated with higher incidence of psoriatic arthritis

Comorbidities

- Presentation of psoriatic arthritis in children
  - Subset of juvenile idiopathic arthritis.
  - Oligoarticular disease affecting the knees and ankles is most common.
  - May affect smaller joints, including the distal and proximal interphalangeal joints of the hands and feet.
  - Enthesitis and axial disease is associated with HLA-B27 haplotype.
  - May be associated with anterior uveitis.
- Metabolic disease
  - Association of psoriasis and cardiovascular disease has been established in adults.
  - There is mounting evidence that children with psoriasis may have an increased risk of obesity, hypertension, dyslipidemia, and diabetes mellitus.
    - Screening and monitoring for these associated conditions may be important.

DIFFERENTIAL DIAGNOSIS

- Psoriatic diaper rash and other forms of inverse psoriasis.
  - Seborrheic dermatitis
  - Langerhans cell histiocytosis
  - *Candida* or bacterial intertrigo
  - Contact dermatitis
- Plaque psoriasis—must be differentiated from other papulosquamous disorders.
  - Atopic dermatitis
    - Psoriatic plaques tend to be more clearly demarcated from surrounding uninvolved skin and usually are less pruritic than atopic dermatitis lesions.
    - Atopic dermatitis lesions lack the characteristic silvery-white scale of psoriasis.
    - Psoriasis tends to localize to the extensors, whereas atopic dermatitis preferentially affects flexural areas.
    - Some children exhibit overlap between psoriasis and atopic dermatitis.
  - Pityriasis rubra pilaris (PRP)
    - Lesions have a classic salmon color.
    - Focal areas of sparing.
    - Follicular accentuation.
    - Juvenile PRP: most difficult condition to differentiate from psoriasis.
      - Biopsy findings, the classic salmon color of PRP lesions, the focal areas of sparing, and follicular accentuation help clinically distinguish this condition from psoriasis.
- Pustular psoriasis.
  - May be confused with disseminated candidiasis or staphylococcal scalded skin syndrome.
  - To differentiate
    - Skin biopsy
    - Gram stain
    - Culture of the contents of several pustules
  - Noninfectious pustular eruptions, such as pustular drug eruptions, may also mimic pustular psoriasis.
  - The history of a recently started medication and a skin biopsy can sometimes help differentiate between pustular psoriasis and a pustular drug eruption.
- Scalp psoriasis.
  - May be mistaken for tinea capitis or seborrheic dermatitis.
  - Potassium hydroxide preparation and a fungal culture of the scale is important to rule out tinea capitis because the treatment for scalp psoriasis (topical corticosteroids) can exacerbate tinea capitis.
- Guttate psoriasis.
  - Pityriasis rosea
  - Tinea corporis
  - Pityriasis lichenoides
  - Secondary syphilis
- Nail changes of psoriasis can be seen in other conditions.
  - Alopecia areata
  - Onychomycosis

DIAGNOSTIC APPROACH

- Issues to address when evaluating a child suspected of having psoriasis
  - Family history of psoriasis
  - Recent history of streptococcal throat or perianal infection
  - Frequency and duration of eruptions
  - Tendency for lesions to appear on traumatized skin (eg, sunburned, scratched, tattooed) (Koebner phenomenon)
  - Nail changes (eg, nail pitting)
  - Behavior of lesions in response to UV light
  - Joint pains
  - Previous treatment modalities and their efficacy

LABORATORY FINDINGS

- Bacterial culture of oropharynx and perianal area; antistreptolysin titer
  - Rules out streptococcal infection, especially in guttate psoriasis; may play a role in pustular psoriasis
- Potassium hydroxide preparation of scale
  - Rules out fungal infection, especially in scalp psoriasis and annular lesions

DIAGNOSTIC PROCEDURES

- Skin biopsy
  - Confirm clinical diagnosis of psoriasis, especially in atypical presentations.

TREATMENT APPROACH

- Psychosocial effect of the disease on the child and the child's family is a critical consideration.
  - Adverse effect on quality of life.
  - Educate the child, siblings, and parents, as well as teachers and classmates, about the nature of psoriasis.

- Give affected families information about available psoriasis support groups.
- Psychological counseling should be sought to equip patients with effective coping skills.

- Identify and eliminate potential triggers or exacerbating factors.
  - Streptococcal infection
  - Medications
    - Lithium
    - β-Blockers
    - Interferon
    - Systemic corticosteroids
  - Stress
  - Skin trauma (Koebner phenomenon: piercings, tattoos, sunburns)
- Topical corticosteroids are the most common treatment.
  - Calcipotriol or calcipotriene can be used alone or in combination with topical corticosteroids
- Less commonly used topical therapies include
  - Anthralin
  - Salicylic acid
  - Tar preparations
  - Topical retinoids
  - Topical calcineurin inhibitors
- Bland emollients are an essential part of the skin care regimen.
  - Moisturization and application of emollients lessens dryness and scaling associated with psoriasis.
  - In most patients, emollients should be used as adjunctive therapy to anti-inflammatory topical medications, although mild psoriasis may improve with emollients alone.

SPECIFIC TREATMENTS

Topical Agents

- Emollients: bland, thick preferred.
- Corticosteroids by class: First-line therapy for all types of psoriasis; apply twice daily for acute management, and then 2–3 days per week (eg, weekends) for maintenance.
  - Class 1 (ultra-potent).
    - Clobetasol propionate 0.05%.
    - Betamethasone dipropionate 0.05%.
    - Reserved for unresponsive, thick psoriatic plaques.
    - Continuous treatment should not last >2 weeks.
  - Class 2 and 3 (medium to high potency).
    - Fluocinonide 0.05%
    - Betamethasone valerate 0.1%
    - Triamcinolone ointment 0.1%
    - Mometasone ointment 0.1%
  - Class 4/5 (medium potency).
    - Hydrocortisone valerate 0.2%
    - Triamcinolone 0.025%
    - Mometasone cream 0.1%
  - Class 6/7 (low potency).
    - Hydrocortisone (all concentrations)
      - Hydrocortisone 2.5% can be used for facial psoriasis but is ineffective in many children.
    - Desonide 0.05% cream, gel, and foam
    - Fluocinolone 0.01% oil and solution (may be useful for mild scalp psoriasis)
  - Side effects of corticosteroids include
    - Possible cutaneous side effects: atrophy, striae, telangiectasia.
    - Possible systemic side effects: hypothalamic-pituitary-adrenal axis suppression, growth impairment, cataracts, glaucoma.
    - Avoid use of high-potency preparations on face and intertriginous areas.
  - Ointment is the preferred vehicle when treating psoriasis.
    - Occlusive effect
    - Increased potency
    - Useful for dry, scaly lesions
  - Gels.
    - Readily absorbed
    - Useful in hairy areas
    - Can cause dryness and irritation
  - Creams.
    - Rub in well.
    - Are aesthetically pleasing.
    - May be less potent than ointment form of same drug.
  - Foams, solutions, and oils can be used on the scalp.
- Calcipotriol or calcipotriene (Dovonex): useful alone in limited disease or useful adjunct to corticosteroids.
  - Can be used once to twice a day.
  - Available as an ointment, cream, or solution.
  - Causes irritation.
  - Combination products with corticosteroids may increase compliance.

- Coal tar preparations: Useful for thicker plaques; apply once to twice daily.
  - Liquor carbonis detergens (LCD) in combination with emollients or corticosteroids
  - Liquid form in bath
  - Side effects
    - Irritation, staining, unpleasant odor, folliculitis
    - Increased risk of irritation on face and intertriginous areas
- Anthralin: Short-contact therapy; large or stubborn plaques; apply for 10 minutes, and then increase duration as tolerated once daily.
  - Drithrocreme
  - Causes irritation and staining of skin and bathtub or sink
- Calcineurin inhibitors.
  - Tacrolimus ointment (Protopic) 0.03% or 0.1%
  - Pimecrolimus cream (Elidel) 1%
  - Side effects
    - Occasional burning or itching with first few applications
    - US Food and Drug Administration black-box warning (theoretical malignancy risk based on oral forms)
- Retinoids: Useful in limited, mild to moderate disease; apply once daily.
  - Tazarotene cream or gel (Tazorac) 0.5% or 0.1%
  - Issues
    - Causes dryness, local irritation
    - Pregnancy category X
- Topical application of oils.
  - Nighttime application, such as fluocinolone or nonsteroidal oils, such as mineral, can be a useful adjunct in treating scalp psoriasis in older children.
  - Can be applied to the scalp at night to loosen adherent scale and then shampooed out in the morning.
    - The addition of low concentrations (5%–6%) with or without tar (5% LCD) can be effective in decreasing scale when used for 1–2 weeks prior to starting a topical steroid regimen.
  - Some black patients prefer greasy scalp preparations (eg, lotions, ointments, oils) rather than foams or gels because the former preparations also lubricate the hair and prevent brittleness and breakage.
- For scalp lesions.
  - Liquid or foam corticosteroid preparations (may cause stinging).
    - Clobetasol foam, solution
    - Fluocinonide solution
    - Fluocinolone solution, oil
  - Tar, zinc, or salicylic acid shampoos.
  - Parents should be warned that these might cause dryness of the hair and scalp.

Phototherapy

- Psoralen plus UV-A
  - Methoxsalen is a photosensitizer.
  - Rarely used in children.
  - Issues include
    - Cataracts
    - Skin aging
    - Skin cancer
    - Expensive
    - Inconvenient
- UV-B
  - Broadband UV-B.
  - Narrow-band UV-B (311–313 nm) (preferred) can clear plaques with lower amounts of UV light.
  - Issues include
    - Can be expensive
    - Inconvenient
    - Skin aging
    - Skin cancer (Data are not conclusive but likely negligible risk.)
    - Difficult for younger patients
- Excimer laser
  - 308 nm
  - Can deliver high-dose UV therapy to affected areas only, sparing normal skin
  - Issues
    - Can be expensive
    - Shares similar concerns for skin cancer and aging as narrow-band UV-B

Systemic Agents

- Methotrexate
  - Indications
    - Recalcitrant widespread psoriasis
    - Erythrodermic psoriasis
    - Pustular psoriasis
    - Psoriatic arthritis
  - Side effects
    - Bone marrow toxicity
    - Hepatotoxicity
    - Nausea

  - Vomiting
  - Must monitor patient's complete blood cell count and liver function tests
- Cyclosporine
  - Indications
    - Quick control over severe psoriasis
    - Recalcitrant widespread psoriasis
    - Erythrodermic psoriasis
    - Pustular psoriasis
  - Side effects
    - Renal and hepatic toxicity
      - Recommended to limit use to 1 year
    - Hypertension
    - Hypertrichosis
    - Gingival hyperplasia
    - Immunosuppression
- Oral retinoids
  - Indications
    - Pustular psoriasis
    - Erythrodermic psoriasis
  - Side effects
    - Cheilitis
    - Xerosis
    - Skin fragility
    - Hypertriglyceridemia
    - Skeletal abnormalities (Chronic use may affect growth.)
    - Teratogenicity (Avoid in adolescent girls.)
- Tumor necrosis factor α inhibitors (etanercept, adalimumab, infliximab)
  - Approved for treatment of severe psoriasis in adults
    - Indications
      - Severe, recalcitrant psoriasis
      - More limited psoriasis with large effect on quality of life
      - Psoriatic arthritis
    - Side effects
      - Injection site reactions.
      - Potential, but unknown, risk of malignancy.
      - Live vaccination should be avoided.
      - Immunosuppression.
      - Caution if congestive heart failure, demyelinating disease, tuberculosis risk factors.

WHEN TO ADMIT

- Widespread pustular psoriasis
- Erythrodermic psoriasis

WHEN TO REFER

- Unresponsive to first- or second-line therapy
- Severe disease (widespread or large effect on quality of life)
- Pustular psoriasis
- Erythrodermic psoriasis
- Worsening joint pains (Refer to rheumatologist.)

COMPLICATIONS

- Possible complications of erythrodermic psoriasis include
  - Electrolyte imbalances
  - Cardiovascular compromise
  - Sepsis
  - Considered a dermatologic emergency

DEFINITION

- Normal puberty
  - Series of complex hormonal changes that begins at 8–13 years of age in girls and 9–14 years of age in boys
- Delayed puberty
  - Girls
    - No breast development by age 13 years
    - Delay >4–5 years from onset of puberty to menarche
  - Boys
    - No testicular enlargement by age 14 years
    - Maturation arrest
- Precocious puberty
  - Appearance of secondary sexual characteristics <8 years in girls and <9 years in boys.
  - Trends toward earlier onset of puberty in girls have led the Pediatric Endocrine Society to publish recommendations that the cutoff age for precocious puberty should be decreased to 7 years in white girls and 6 years in black girls unless
    - The tempo of puberty is abnormal.
    - The bone age is advanced >2 years.
    - The predicted height is <150 cm (59").
    - Focal neurologic deficits are present.
    - Headaches are present.
    - The family's or child's emotional state is adversely affected.
  - The recommendations remain controversial.
- Variations of puberty
  - Premature thelarche
    - Isolated premature breast development
  - Premature adrenarche
    - Isolated premature development of sexual hair

HISTORY

- History related to possibly abnormal puberty should include thorough review of
  - Child's medical history, with emphasis on growth, development, significant illnesses, and signs and symptoms related to the endocrine and central nervous systems
  - Exposure to medications and other exogenous agents that can affect puberty
  - Family history of pubertal onset and progression

PHYSICAL EXAMINATION

- Physical examination related to possibly abnormal puberty should include careful
  - Measurement of growth parameters, with calculation of growth velocity
  - Determination of Tanner staging
  - Attention to the endocrine and central nervous systems

DIFFERENTIAL DIAGNOSIS

Delayed Puberty

- Constitutional delay
- Deficiency of gonadotropin-releasing hormone (GnRH) secretion by the hypothalamus
  - Genetic and molecular causes
    - Isolated deficiency
    - Kallmann syndrome
    - Laurence-Moon/Bardet-Biedl syndromes
    - Prader-Willi syndrome
  - Acquired causes
    - Infection
    - Neoplasm
    - Infiltrative disease
    - Trauma
- Deficiency of gonadotropin secretion by the pituitary
  - Genetic
    - Panhypopituitarism (including transcription factor mutations in *PROP1, HESX1*, and *LHX3*)
    - Isolated deficiency
    - Fertile eunuch (normal follicle-stimulating hormone level, low luteinizing hormone level)
    - Leptin or leptin-receptor deficiency
  - Acquired
    - Infection
    - Tumor
    - Excess prolactin secretion, adenoma
    - Trauma
- Gonadal disorders
  - Genetic and molecular
    - Turner syndrome (45,X or structural X abnormalities or mosaicism)
    - Klinefelter syndrome (47,XXY)
    - Noonan syndrome
    - Syndromes of complete androgen insensitivity (no sexual hair)
    - Sertoli-cell–only syndrome (also called del Castillo syndrome)
    - Pure gonadal dysgenesis
    - Myotonic dystrophy
    - Receptor mutations
  - Acquired
    - Gonorrhea (male)
    - Virus (mumps, coxsackie)
    - Tuberculosis (male)
    - After radiation or chemotherapy
    - Torsion

- — Surgery
- — Congenital anorchia (vanishing testes syndrome)
- — Autoimmune

- Adrenal and gonadal steroid enzyme deficiencies
- Malnutrition
- Excessive exercise
- Chronic systemic diseases
  - Congenital heart disease
  - Chronic pulmonary disease
  - Inflammatory bowel disease, celiac disease
  - Chronic renal failure and renal tubular acidosis
  - Hypothyroidism
  - Poorly controlled diabetes mellitus
  - Sickle cell anemia, thalassemia
  - Collagen-vascular disease
  - Anorexia nervosa
  - HIV infection

Isosexual Precocious Puberty

- Central (with pituitary gonadotropin secretion)
  - Idiopathic
    - — Diagnosis is made only after a search for a pathologic cause is negative.
  - Central nervous system abnormalities
    - — Congenital anomalies (hydrocephalus)
      - Tumors (hypothalamic, pineal, other)
      - Hamartoma
      - Postinflammatory condition
      - Trauma
      - Neurofibromatosis
      - Tuberous sclerosis
      - Hypothyroidism (severe)
- Peripheral
  - Exogenous sex steroids
    - — Both testes are small.
  - Gonadal tumors or cysts
  - Adrenal hyperplasia or tumor
    - — Both testes are small.
  - Ectopic gonadotropin–secreting tumors (chorioepithelioma, hepatoblastoma, teratoma)
    - — Both testes are of pubertal size.
  - Familial Leydig cell hyperplasia, receptor mutation
  - Albright syndrome, G-protein mutation

Heterosexual Precocious Puberty

- Girls
  - Congenital adrenal hyperplasia
  - Androgen-secreting tumors
    - — Adrenal
    - — Ovarian
    - — Teratoma
  - Exogenous androgens
- Boys
  - Estrogen-producing tumors
    - — Adrenal
    - — Teratoma
    - — Hepatoma
    - — Testicular
  - Exogenous estrogens
  - Increased peripheral conversion of androgens to estrogens

Gynecomastia

- Occurs in about 40% of healthy boys
- Klinefelter syndrome
- Partial androgen insensitivity syndrome
- Hyperprolactinemia
- Liver disorders
- Adrenal carcinoma
- Biosynthetic defects in testosterone production
- Androgen receptor defects
- Increased activity of peripheral aromatase
- Certain drugs
  - Estrogen-like effect.
    - — Diethylstilbestrol
    - — Oral contraceptive pills
    - — Digitalis
    - — Estrogen-containing cosmetics
  - Increase estrogen formation.
    - — Gonadotropins
    - — Clomiphene
  - Inhibit testosterone action.
    - — Ketoconazole
    - — Spironolactone
    - — Cimetidine
    - — Isoniazid
    - — Methyldopa
    - — Captopril
    - — Tricyclic antidepressants
    - — Diazepam
    - — Marijuana
    - — Phenothiazine

Adrenarche

- An abnormal androgen source (eg, tumor, late-onset congenital adrenal hyperplasia) must be excluded.
- May occur in children with neurologic problems.

LABORATORY EVALUATION

- Evaluation for delayed puberty
  - Initial screening tests
    - — Luteinizing hormone, follicle-stimulating hormone

- Testosterone or estrogen, depending on gender
- Thyroid-stimulating hormone, thyroid hormone
- If systemic disease is thought to exist
  - Complete blood cell count
  - Erythrocyte sedimentation rate, C-reactive protein
  - Comprehensive panel (electrolytes; renal and liver function tests)
  - Insulin-like growth factor 1, insulin-like growth factor binding protein 3
  - Urinalysis
  - Celiac disease panel (anti-endomysial immunoglobulin A [IgA] antibody or tissue transglutaminase IgA and total IgA levels)
  - Inflammatory bowel disease panel
  - Prolactin

- Other tests (if indicated)
  - Karyotype
  - GnRH or GnRH analogue stimulation test

- Evaluation for precocious puberty
  - Initial screening tests.
    - Luteinizing hormone, follicle-stimulating hormone
    - Estradiol, testosterone
    - Dehydroepiandrosterone sulfate
    - 17-Hydroxyprogesterone
    - Thyroid-stimulating hormone, thyroid hormone
  - Secondary tests (if indicated).
    - Serum β-human chorionic gonadotropin
    - GnRH
  - Measurement of serum gonadotropin levels before and after injection of GnRH usually distinguishes central from peripheral precocious puberty.
- Gynecomastia
  - Initial screening blood work when clinically indicated
    - Testosterone
    - Estradiol
    - Luteinizing hormone
    - Follicle-stimulating hormone
    - Prolactin
    - β-Human chorionic gonadotropin level
    - Liver function tests

IMAGING

- Evaluation for delayed puberty and precocious puberty can include, if indicated
  - Bone age
  - Brain magnetic resonance imaging
  - Pelvic ultrasonography

SPECIFIC TREATMENT

Delayed Puberty

- Treatment is directed toward the cause when possible.
- In all cases, provide strong psychological support to the adolescent and family.
- Gonadal failure or gonadotropin deficiency.
  - Treatment focuses on replacing the appropriate sex steroid.
- Constitutional delay.
  - Waiting may be the best course.
  - Boys.
    - A short course of low-dose injectable testosterone (eg, 50–100 mg monthly for 4 doses) if delayed development affects psychological well-being
  - Girls.
    - Cosmetic treatment (eg, padded bra)
    - Estrogen therapy necessary only occasionally
- GnRH or gonadotropin deficiency.
  - Fertility may be induced with GnRH or gonadotropin therapy.
- Strong psychological support must be provided.

Isosexual Precocity

- Suppression or removal of underlying cause
- Idiopathic central precocious puberty
  - GnRH analogues lead to pituitary desensitization and reduce gonadotropin secretion to prepubertal levels.
  - Available intramuscularly (depot), subcutaneously, and intranasally.
  - Depot leuprolide is used most commonly in the United States.
    - Usually given every 3–4 weeks.
    - Longer-acting forms given every 12 weeks are available.
    - Has been used for years, is effective, and has minimal side effects.
- Gonadotropin-independent precocious puberty
  - Testolactone and other aromatase inhibitors (anastrozole, letrozole)
  - Spironolactone (androgen receptor inhibitor)
  - Ketoconazole (steroidogenesis inhibitor)
- Albright syndrome
  - Tamoxifen (estrogen receptor inhibitor)

Heterosexual Precocious Puberty

- Removal of sex hormone source (exogenous or tumor)
- Suppression with glucocorticoid replacement therapy (congenital adrenal hyperplasia)

Gynecomastia

- Treatment in most cases is reassurance.
- For unresolved or rapidly developing cases
  - Medical therapy.
    - Clomiphene (antiestrogen).
    - Tamoxifen (estrogen antagonist).
    - Testolactone (peripheral aromatase inhibitor).
    - Danazol (synthetic derivative of testosterone).
    - No randomized, controlled trials have assessed these drugs.
  - Surgical intervention remains the mainstay of treatment.

Isolated Premature Thelarche and Adrenarche

- No treatment is required.

WHEN TO REFER

- Delayed puberty
  - No breast development in girls by 13 years of age
  - No menarche 4–5 years after onset of breast development or by 15–16 years of age in girls
  - No testicular enlargement in boys by 14 years of age
  - Maturational arrest
  - Hormonal abnormalities identified by initial screening tests
  - Parental or physician discomfort
- Precocious puberty
  - Signs of puberty <6–8 years in girls
  - Signs of puberty <9 years in boys
  - Rapidly progressive puberty (eg, stage 3 breast when first noted)
  - Heterosexual precocious puberty
  - Hormonal abnormalities identified by initial screening tests
  - Parental or physician discomfort
- Gynecomastia
  - Does not resolve after 2 years
  - Develops rapidly

FOLLOW-UP

- Premature thelarche and premature adrenarche
  - Careful follow-up physical examinations are necessary to ensure they do not represent early stages of complete sexual precocity.

PROGNOSIS

- Precocious puberty
  - Can significantly reduce adult height.
  - Sometimes adversely affects the child's and family's emotional state.
- Adrenarche
  - May be a marker of future polycystic ovary syndrome
- Gynecomastia
  - Usually resolves within 2 years

DEFINITION

- Pyloric stenosis (PS) is a condition characterized by abnormal thickening of the antropyloric muscles.

SIGNS AND SYMPTOMS

- Typical presentation is projectile, non-bilious vomiting in a full-term male infant between 3 and 6 weeks of age.
- Common age of symptom manifestation is 3–6 weeks.
  - Has been reported in newborns and older infants
- Vomiting.
  - Initially, the infant vomits a small amount of food immediately after feeding and continues to gain weight.
  - After a few weeks, vomiting becomes more frequent and projectile and occurs after every feeding.
  - The vomitus is usually non-bilious but may become coffee-ground colored with the development of gastritis and bleeding.
  - The infant continues to be hungry immediately after vomiting.
- The infant may subsequently develop gastritis.
- Infants are usually active and alert.
- Lethargy ensues only after significant dehydration.
- Physical examination reveals weight loss and dehydration.
- The enlarged pylorus may be felt as a firm, mobile, ovoid-shaped mass—the so-called olive.
  - If the infant is relaxed, the mass can be felt in ~80%–90% of cases.
  - The infant's feet should be elevated.
  - The knees should be placed in the flexed position to relax the abdominal muscles.
  - 2 or 3 fingertips are placed in the right upper quadrant, gently advanced into the deeper tissues below the liver edge, and then slowly swept toward the umbilicus.
    - The mass can be felt to roll under the fingertips during this sweeping motion.
  - The mass is rarely palpable in an agitated, crying infant with a contracted abdominal wall.
  - The mass can be best felt immediately after an episode of projectile emesis when pylorus is fully contracted and at its firmest consistency.
  - If the mass is not felt with the infant in the supine position, palpation while the infant is lying prone may be successful.
  - Occasionally, the primary care physician may need to
    - Pass a nasogastric tube.
    - Empty the stomach.
    - Feed the infant small quantities of dextrose in water to help relax the abdominal wall.
- Gastric contractions, which move across the upper abdomen from left to right, may be seen in some infants.
  - Best observed with a bright light directed across the abdomen from the patient's side.
  - The examiner should stand at the foot of the examining table.

DIFFERENTIAL DIAGNOSIS

- Other causes of gastric outlet obstruction should be considered in the differential diagnosis of an infant with non-bilious emesis.
  - Foregut stenosis.
  - Gastric duplications.
  - Antral webs.
  - Pylorospasm.
  - Annular pancreas.
  - Malrotation.
  - Many of these causes can be excluded by ultrasonography or an upper gastrointestinal (GI) tract series.
- When a diagnosis of PS cannot be established in an infant with persistent emesis and a normal ultrasound and upper GI tract series, the following possibilities should be considered:
  - Poor feeding regimen
  - Gastroesophageal reflux
  - Sepsis
  - Intracranial disease
  - Renal disorder
  - Adrenal insufficiency
    - Salt-losing congenital hyperplasia.
    - Prompt diagnosis and immediate therapy are crucial.
    - This condition should be suspected in an infant with
      - Abnormal genitalia
      - Hyponatremia
      - Hyperkalemia
- When the workup is inconclusive, reevaluating in a week to 10 days is reasonable.

DIAGNOSTIC APPROACH

- Palpation of a mass on physical examination alone should aid in making an accurate diagnosis in most patients.
- Once the mass is felt unequivocally, the diagnosis of PS is established and no further diagnostic maneuvers are necessary.
- A large volume of fluid aspirated from the stomach of a fasting infant who has a history of projectile vomiting strengthens the possibility of PS.

LABORATORY FINDINGS

- Persistent vomiting caused by gastric outlet obstruction results in the continuous loss of gastric hydrochloric acid.
- Dehydration causes an increase in aldosterone production, leading to increased renal excretion of potassium.
- Loss of hydrochloric acid and potassium results in a hypochloremic, hypokalemic metabolic alkalosis.
- Depletion of chloride in the blood leads to an exchange of hydrogen and potassium for sodium in the distal tubule, resulting in a paradoxical aciduria.
- A spectrum of electrolyte abnormalities may be seen.
  - Hypoglycemia may be present and may cause seizures.
  - Unconjugated hyperbilirubinemia is common.
    - Correlates with a decrease in hepatic glucuronosyl transferase activity
    - Resolves after treatment

IMAGING

- Palpation of a mass on physical examination alone should aid in making an accurate diagnosis in most patients.
- Increasing reliance is now placed on noninvasive, highly accurate, and relatively inexpensive radiologic tests, such as ultrasonography.
- Ultrasonography.
  - Sensitivity approaches 100%.
  - The most useful technique to confirm the diagnosis in cases in which
    - PS is suspected clinically.
    - Hypertrophied pylorus cannot be palpated.
  - Measurement of pyloric wall thickness, diameter, and pyloric channel length accurately establishes the diagnosis of PS.
    - Pyloric muscle wall thickness ≥3.7 mm and a channel length ≥17 mm have been shown to have ≥90% positive predictive value.
    - Diagnostic criteria for wall thickness may be reduced to 3 mm in neonates <30 days.
- Upper GI tract contrast study.
  - May be performed when ultrasonography is not diagnostic
  - Characteristic upper GI tract findings in infants with PS include
    - An elongated and narrowed pyloric channel (string sign)
    - The shoulders of the hypertrophied pylorus bulging into the intestinal lumen

TREATMENT APPROACH

- Management of PS consists of hydration and pyloromyotomy.

SPECIFIC TREATMENTS

Preoperative Management

- In the past, infants often had overwhelming malnutrition and electrolyte abnormalities.
- In the current era of early diagnosis, infants infrequently progress to this severe state.
- Anatomic correction of PS is not a surgical emergency.
- Although PS is a form of intestinal obstruction, gangrene and intestinal perforation do not occur.
- Infants should not undergo surgery until fluid and electrolyte deficits have been corrected.
- If infants undergo surgery with uncorrected alkalosis, the profound stress of surgery on urinary excretion of sodium may intensify electrolyte abnormalities.
- Fluid replacement should include deficit correction and daily maintenance fluids.
  - Continuous maintenance infusion of 5% dextrose in 0.45 normal saline
  - Addition of 20 mEq/L potassium chloride once urine output is established
  - Repeated boluses of isotonic sodium chloride at 20 mL/kg until a serum chloride level of 100 mEq/L is achieved
  - Prior to anesthesia and surgery
    - Nasogastric decompression should be performed.
    - Fluid and electrolyte deficits should be corrected.

Surgical Management

- Surgical myotomy is reliable and safe.
- Once the volume and electrolyte status is corrected, the infant is ready for surgery.

- Ramstedt operation (pyloromyotomy) through a right upper quadrant transverse incision has been the traditional treatment for hypertrophic PS.
- New alternative approaches include
  - Circumumbilical
  - Laparoscopic
    - Shorter mean operative time
    - No increase in complications or costs
    - Randomized controlled trials indicate
      - Lower rate of wound-related complications
      - Decreased time to full feeding
      - Reduced length of postoperative stay

Postoperative Management

- Postoperative vomiting occurs in most infants.
  - Will usually subside by the second to fifth feeding
- Parental education on postoperative vomiting is important before surgery.
- Infants should be fed full-strength formula or human milk every 3–4 hours starting 6 hours after surgery.
- In case of emesis, infants can be refed the amount vomited 1 hour later, with resumption of the feeding schedule thereafter.
  - Early refeeding has resulted in a reduction in the postoperative hospital stay.
- Discharge criteria.
  - Infants are usually discharged 24–48 hours after surgery.
  - Feeding tolerance must be reassessed before discharge.

Medical Management

- Medical management alone has been largely discarded.
- May be considered as an alternative to pyloromyotomy, particularly in children with major concurrent primary disease.
- The anticholinergic agent atropine sulfate has been used with success.
  - Prolongs the duration of hospital stay.
  - Studies comparing predominantly oral atropine sulfate with surgical myotomy have reported similar success rates.

WHEN TO ADMIT

- All infants need to be hospitalized to correct electrolyte imbalance and for surgery.

WHEN TO REFER

- All infants with PS should be referred to a surgeon.

COMPLICATIONS

- Intraoperative and early postoperative complications
  - General
    - Morbidity and mortality from surgical repair
      - Have decreased from 50% to <1%
    - Negligible risk of
      - Intestinal perforation
      - Hemorrhage
      - Wound dehiscence
      - Postoperative infection
  - Hypoglycemia
    - Reactive hypoglycemia
      - Reported in infants who have a wide variety of medical and surgical conditions.
      - May cause respiratory arrest and death.
      - Constant infusion of dextrose results in hyperinsulinemia.
        - May result in severe hypoglycemia if suddenly terminated before adequate oral feeding is established.
      - Particularly likely if liver glycogen stores have been depleted, as has been shown in infants with PS.
  - Death
    - Mortality is <0.1%.
    - Potential causes of death include
      - Delayed diagnosis
      - Inadequate preoperative rehydration
      - Pulmonary aspiration
      - Unrecognized perforation
      - Hypoglycemia
      - Persistent obstruction
      - Hemorrhage
      - Presence of other associated congenital anomalies
- Late complications
  - Postoperative obstruction
    - Radiographic evaluation is necessary if vomiting persists beyond 5–7 days.
    - Excessive vomiting may be caused by
      - Persistent stenosis
      - Gastroesophageal reflux
      - Gastric outlet obstruction
      - Small-bowel obstruction attributable to adhesions
    - Upper GI tract contrast series is difficult to interpret but may be helpful.

- Narrowing and elongation of the pyloric channel.
  - Usually persist for weeks to months after a successful operation, even in infants who have minimal or no postoperative vomiting
- Subsequent operation may be indicated in the rare event of persistent pyloric obstruction.

PROGNOSIS

- The long-term outcome for patients treated for PS is excellent.
- Rapid gastric emptying and duodenogastric reflux have been identified in some patients who had undergone pyloromyotomy 5–7 years earlier.
  - Other studies have shown no differences between previous patients with PS and controls after long-term follow-up.

DEFINITION

- Normal pattern of infections in childhood.
  - Healthy children experience 6–8 upper respiratory tract infections per year in the first few years after birth.
  - Up to 15 infections per year can still be within the reference range.
  - The high frequency of infections results from immunologic immaturity and frequent exposure to respiratory pathogens.
    - Attendance in child care and exposure to secondhand smoke may increase the number of infections.
- Recurrent infections may be a sign of an underlying, possibly immunologic, disorder.
  - This is much less common than "normal" childhood infections.
  - Early identification of these children is critical.
  - Prompt intervention can decrease morbidity and mortality.

HISTORY

- A complete history should be obtained for all children being evaluated for recurrent infections.
- Document characteristics of previous infections.
  - Types of pathogens and infections
  - Duration of illnesses
  - Need for hospitalization
- Detailed family history is important.
  - Many of the primary immunodeficiencies are hereditary.
- History of risk factors for HIV infection.
  - Personal for adolescents
  - Parental when congenital transmission is a possibility
  - Drug use
  - Prostitution
  - Blood-product transfusion
  - Multiple sexual partners
  - History of sexually transmitted infection
  - Homosexual behavior
- Obtain a complete review of systems.
  - Pay attention to known associated features of immunodeficiency syndromes.
    - Failure to thrive
    - Intractable diarrhea and malabsorption
    - Rheumatologic conditions
    - Hepatosplenomegaly
    - Lymphadenopathy
    - Absence of lymph tissue
    - Thrombocytopenia
    - Eczema
    - Oculocutaneous albinism
- Immunization history.
  - Failure to make protective antibodies in response to immunizations can be indicative of immunodeficiency.
- Infections associated with an underlying immune disorder may present in various ways.
  - Increased frequency of common infections
  - Repeated serious bacterial infections
- Immunodeficiency may cause a common infection to
  - Have increased severity.
  - Have prolonged duration.
  - Fail to respond to appropriate treatment.
- Immunodeficiency may cause a common infection to present at an uncommon age.
  - Thrush or candidal diaper dermatitis in children >1 year suggests a defect in T-cell immunity.
- Immunodeficiency may produce an infection with an opportunistic pathogen.
  - *Pneumocystis jiroveci*
  - *Cryptococcus neoformans*
- Immunodeficiency may become apparent as an infection after the administration of a live virus vaccine (rare).

PHYSICAL EXAMINATION

- A complete physical examination should be performed.
- Children with immunodeficiency appear chronically ill.
- Growth parameters should be obtained to determine the presence of failure to thrive.
  - Height
  - Weight
  - Head circumference
- Physical signs that may indicate underlying immunodeficiency.
  - Absence of tonsils
  - Presence of generalized lymphadenopathy and hepatosplenomegaly
  - Skin lesions
    - Eczema
    - Abscesses
    - Seborrhea
  - Mucous membrane involvement
    - Telangiectasias
    - Mucositis
- Look for signs of recurrent infection.
  - Dull, retracted tympanic membranes
- Look for evidence of ongoing infection.
  - Thrush

- Note any specific or abnormal signs or symptoms that may be associated with a particular immunodeficiency syndrome.
  - Intractable diarrhea and malabsorption
    - Severe combined immunodeficiency (SCID), X-linked agammaglobulinemia (XLA), common variable immunodeficiency
  - Rheumatologic conditions
    - Common variable immunodeficiency, immunoglobulin A (IgA) deficiency, XLA
  - Hepatosplenomegaly, lymphadenopathy
    - Hyper-IgM syndrome
  - Absence of lymph tissue
    - XLA
  - Thrombocytopenia
    - Wiskott-Aldrich syndrome
  - Eczema
    - Wiskott-Aldrich syndrome, chronic granulomatous disease, hyper-IgE syndrome (Job syndrome)
  - Oculocutaneous albinism
    - Chédiak-Higashi syndrome

DIFFERENTIAL DIAGNOSIS

Secondary Immunodeficiency

- Infection
  - HIV
  - Congenital rubella
  - Other viral infections (eg, influenza)
- Cancer
  - Leukemia
  - Lymphoma
- Medication
  - Cytotoxic
  - Immunosuppressive
  - Corticosteroids
- Malnutrition
  - Protein, mineral, or vitamin deficiency
- Splenic dysfunction
  - Splenectomy
  - Sickle cell disease
  - Congenital asplenia
- Metabolic disorders
  - Uremia
  - Protein-losing enteropathy
  - Diabetes
  - Galactosemia
- Chromosomal
  - Down syndrome
  - Bloom syndrome
- Improvements in medical care
  - Organ transplants
  - Cancer chemotherapy
  - Anti-cytokine therapies
    - Anti–tumor necrosis factor-α for rheumatoid diseases and Crohn disease have been associated with an increased susceptibility to tuberculosis and histoplasmosis.
  - Implants
    - Heart valves
    - Catheters

Primary Immunodeficiency

- Evaluation of the child for a primary immunodeficiency should be considered after non-immunologic and secondary immunodeficiency syndromes have been ruled out.
- Most children are symptomatic within the first few years of life, except in
  - Common variable immunodeficiency
  - Deficiencies of the terminal complement components
- Primary immunodeficiency may involve the innate or adaptive immune system.
  - Increased recognition of primary immune deficiency states, including defects in innate and cellular immune responses
  - Improved understanding of the basis of immunodeficiency for certain syndromes
- Specific timing of infections may serve as a clue to the nature of immunodeficiency.
  - Antibody deficiency states are not generally recognized within the first few months of life because maternal antibody is present.
  - SCID, complete DiGeorge syndrome, congenital neutropenia, and leukocyte adhesion defect typically present with infections early in life.
- Primary immunodeficiency is classified by the specific component of the immune system that is affected.
  - Humoral (**Table 1**)
    - The antibody-mediated arm of the immune system.
    - Represents 50%–70% of symptomatic primary immunodeficiencies.
    - Children are susceptible to recurrent sinopulmonary infections with encapsulated bacteria.
      - *Streptococcus pneumoniae*
      - *Haemophilus influenzae*

Table 1. Humoral Immunodeficiencies

Syndrome	Clinical Features	Associated Features
X-linked agammaglobulinemia	Susceptibility to encapsulated bacterial pathogens Sinopulmonary and gastrointestinal infections, sepsis, meningitis Enhanced susceptibility to enterovirus and rotavirus Symptomatic poliovirus infection following live poliovirus vaccination	Asymmetric arthritis, dermatomyositis, malabsorption, absence of tonsils, adenoids, and lymph nodes
Transient hypogammaglobulinemia of infancy	Recurrent sinopulmonary infections; generally improves by 3–4 y	May develop IgA deficiency
Hyper-IgM syndrome	X-linked Recurrent bacterial infections, including encapsulated pathogens Infections associated with T-cell defects (eg, *Pneumocystis jiroveci*) also seen	Low levels of IgG, IgA, and IgE Neutropenia, thrombocytopenia, T-cell defects
Common variable immunodeficiency	Sinopulmonary infections Bronchiectasis Giardiasis	Most common in second and third decade Noncaseating granulomas, malabsorption, autoimmune disease
IgA deficiency	Very common (1 in 400 individuals) but usually asymptomatic Recurrent pulmonary infections leading to bronchiectasis	Systemic lupus erythematosus, rheumatoid arthritis, chronic diarrhea Allergic reactions to gammaglobulin preparations IgG subclass deficiency in some
Specific antibody deficiency with normal immunoglobulins	Recurrent bacterial infections of the respiratory tract	
IgG-subclass deficiency	Normal immunoglobulin levels but with impaired antibody responses to polysaccharide antigens Clinical significance not well delineated	

- Combined defects in cellular and humoral immunity (**Table 2**).
  - The second largest group of primary immunodeficiencies.
  - In addition to bacterial infections, affected children are characteristically more susceptible to fungal, mycobacterial, and viral infections.

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Table 2. Combined Immunodeficiencies

Syndrome	Clinical Features	Associated Features
DiGeorge syndrome	Clinically variable Increased incidence of viral and fungal infections	Hypocalcemia, hypoparathyroidism, congenital heart disease, abnormal facies
Severe combined immunodeficiency (SCID)	B-cell and T-cell deficiencies present Includes a variety of disorders that have multiple modes of inheritance Presents early in life (within first 3 mo) with recurrent or severe infections with all types of pathogens	Failure to thrive, diarrhea Most common (50%) form is X-linked. Thymic hypoplasia Cartilage-hair hypoplasia with certain forms of SCID At increased risk for graft-versus-host disease with red blood cell transfusions
Ataxia telangiectasia	Recurrent sinopulmonary infections	Truncal ataxia, intellectual disability, thymic hypoplasia, telangiectasia of skin and conjunctiva, glucose intolerance, increased risk for malignancy
Wiskott-Aldrich syndrome	Recurrent sinopulmonary infections	Eczema, thrombocytopenia, increased risk for malignancy

- May experience recurrent or persistent candidiasis.
  - Thrush.
  - Diaper candidiasis.
  - Common viral infections of childhood may cause severe or recurrent disease in affected children.
    - Varicella, for example

- Complement deficiency.
  - Least common among the primary immunodeficiencies
  - Occurs in older children and adolescents
    - May experience recurrent meningococcal infection: meningitis or meningococcemia.
    - Children may also have gonococcal arthritis.
- Phagocytic dysfunction.
  - Absence of a particular cell type: neutrophils or monocytes
    - Congenital neutropenia
    - Cyclical neutropenia
  - Defects in chemotaxis
    - Leukocyte adhesion disorder
  - Defects in effector function
    - Chronic granulomatous disease
  - Children typically experience
    - Recurrent skin infections
    - Abscesses
    - Sinopulmonary infections
    - Poor wound healing
    - Delayed umbilical cord separation
    - Gingivitis
    - Eczema

Misdiagnosis of Allergic Conditions

- Allergic conditions may be confused with recurrent infections.
  - Allergic rhinitis misdiagnosed as recurrent upper respiratory tract infection
  - Asthma misdiagnosed as recurrent pneumonia

LABORATORY EVALUATION

- Laboratory evaluation should be guided by the type of infections the child is experiencing.
- Initial screening tests usually include
  - Complete blood cell count and differential
  - Serum Ig levels (IgG, IgA, and IgM)
  - HIV serology, as indicated by the history and physical findings
- Tests of humoral immunity.
  - B-cell count
  - IgG subclass determinations
  - Antibody titers against protein (diphtheria, tetanus toxoid) and polysaccharide (*Pneumococcus, Haemophilus*) antigens
    - Antibody levels must be interpreted with respect to age-appropriate values.
    - High or low levels can be significant.

- Tests of cellular immunity.
  - Delayed-type hypersensitivity skin test (Skin testing may not be reliable <1 year.)
  - Lymphocyte count
    - Total lymphocyte count is obtained by multiplying the total leukocyte count by the percentage of lymphocytes.
    - A value <1,500 cells/μL is considered lymphopenia.
- Phagocytic (macrophage or neutrophil).
  - Complete blood cell count
    - Neutrophil count may be abnormal.
  - IgE level
    - Elevated in hyper-IgE syndrome (Job syndrome)
  - Nitroblue tetrazolium test
  - Flow cytometric respiratory burst assay
- Complement.
  - CH_{50} assay
  - Screening assay for components of classic complement pathway
- Antibody and T-cell studies must be analyzed in the context of age-adjusted normal values.
  - May be affected by acute illness
- Delayed-type hypersensitivity responses are unreliable in infants <1 year.

IMAGING

- Radiologic studies are used primarily in the diagnosis or management of associated infections.
  - The absence of a thymic shadow can be indicative of DiGeorge syndrome or SCID.

TREATMENT APPROACH

- Pending a complete immunologic evaluation, children who are thought to have immunodeficiency syndromes should not receive live attenuated vaccines, such as varicella, rotavirus, and measles-mumps-rubella, to avoid the possibility of vaccine-associated infection.
  - Vaccine recommendations for specific immunodeficiencies can be found in *Red Book: Report of the Committee on Infectious Diseases*.
- Treatment of primary immunodeficiency is condition specific.

SPECIFIC TREATMENT

Intravenous Immunoglobulin (IVIG)

- Patients with humoral and combined immunodeficiencies may benefit from IVIG as replacement therapy.
  - Initial regimen is 300–400 mg/kg every 3–4 weeks.
  - Should be adjusted on the basis of the patient's response.
  - The trough concentration of antibody should be ≥500 mg/dL.
  - Replacement IVIG is not indicated for all types of humoral deficiency.
    - Patients with IgA deficiency may develop anaphylaxis to certain brands of IVIG that contain small amounts of IgA.

Other Therapies

- Bone marrow transplantation
  - SCID
  - Wiskott-Aldrich syndrome
  - DiGeorge syndrome
- Enzyme replacement
  - Certain forms of SCID
- Cytokine therapy
  - Interleukin 2 deficiency
- Interferon gamma treatment
  - Decreases the number of infections in patients with chronic granulomatous disease
- Blood transfusion
  - When needed, should be with cytomegalovirus-negative, irradiated cells to prevent graft-versus-host disease

WHEN TO REFER

- Referral to an immunologist or infectious disease specialist should be considered in the following cases:
  - Recurrent serious bacterial infections
    - Sepsis
    - Pneumonia
    - Meningitis
  - Serious bacterial infection in the context of failure to thrive
  - Infection with an opportunistic pathogen
    - *Pneumocystis*
    - *Cryptococcus*
  - Vaccine-associated infection
  - Unusual age for infection
    - Zoster
    - Thrush
  - Unusual severity or chronicity for a given infection
  - Family history of immunodeficiency

WHEN TO ADMIT

- All patients with severe infections, infections with an unusual organism, or infections requiring intravenous antibiotics
- Patients suspected of having severe immunodeficiencies, such as SCID or Wiskott-Aldrich syndrome

PROGNOSIS

- Prognosis depends on the type of immunodeficiency and promptness of diagnosis and management of these conditions.

PREVENTION

- The genetic basis for many of the primary immunodeficiencies is now known, and prenatal screening is increasingly available.

DEFINITION

- Red eye, pinkeye, or conjunctivitis in children can be difficult to diagnose and manage.
  - Many possible causes, variable presentations, and severity ranging from asymptomatic to vision threatening

HISTORY

- A detailed history should be obtained, with specific attention paid to
  - Onset and progression of the redness
  - Prior episodes of redness
  - Possible trauma or injury
  - Prior ocular surgery
  - Use of contact lenses
  - Personal contact with similarly affected individuals
- Symptoms may include
  - Itching
  - Pain
  - Photophobia
  - Visual disturbance
  - Tearing
  - Mucus discharge
  - Nasal discharge
  - Fever
- When both eyes are affected, sequence and timing of symptom onset are important.

PHYSICAL EXAMINATION

- Location provides clues to the underlying problem.
  - Eyelid
    - Preseptal cellulitis
    - Orbital cellulitis
    - Eyelid tumors
    - Allergic dermatitis
    - Chalazia and hordeola
    - Blepharitis
    - Eyelid trauma
  - Conjunctiva
    - Viral
    - Bacterial
    - Chemical
    - Allergic
    - Vernal
    - Phlyctenulosis
    - Subconjunctival hemorrhage
    - Papilloma
  - Cornea
    - Abrasion
    - Corneal infection: bacterial, viral, fungal, or parasitic
    - Foreign body
  - Intraocular
    - Iritis, uveitis
    - Hyphema
  - Focal inflammation over involved area
    - Scleritis
    - Episcleritis
    - Ocular myositis
- Test visual acuity.
- Examine ocular structures with a penlight looking for
  - Lids: redness, crusting, clogging.
  - Meibomian glands: redness or thickening at the lid margin.
  - Conjunctiva: including everting the lids, looking for a foreign body, and then determining whether redness is diffuse or sectoral.
    - Fine follicles in the conjunctiva overlying the lid indicate a viral infection.
    - Edema suggests allergic conjunctivitis.
  - Cornea: opacities, foreign bodies, disruption of light reflex.
    - Use of fluorescein and a cobalt blue light can highlight any corneal abrasions.
  - Pupils: check size, shape.
    - Mid-dilated pupil suggests iritis.
    - Irregular pupil suggests trauma and possible intraocular foreign body.
- Beyond the eye.
  - Preauricular lymph nodes suggest viral conjunctivitis.
  - Stiff or tender joints suggest juvenile idiopathic arthritis.

DIFFERENTIAL DIAGNOSIS

Eyelid Abnormalities

- Preseptal cellulitis
  - Signs include
    - Tenderness
    - Conjunctival swelling
  - Occurs anterior to the orbital septum and, therefore, has *no* associated double vision, decreased vision, proptosis (eyeball pushed forward), limited motility, or pain with eye movement
  - Common causes
    - Trauma (laceration, insect bite, or puncture wound)

  - Adjacent infections (sinusitis, herpetic dermatitis, infected chalazion, or dacryocystitis)
- Orbital cellulitis
  - Signs may include
    - Tenderness
    - Conjunctival swelling and redness
    - Double vision
    - Decreased vision
    - Proptosis
    - Limited motility
    - Pain with eye movement
    - Fever
    - Pupillary involvement, in severe cases
  - Vital signs, mental status, neck flexibility, and facial sensation should be evaluated.
  - The most common cause is concomitant sinus disease with penetration through the thin bones of the orbital walls.
    - Can also result from dental infection, hematogenous spread, or orbital trauma
- Eyelid tumors
  - Capillary hemangiomas and port-wine stain of Sturge-Weber syndrome can cause redness and lid swelling.
    - These conditions progress slowly over months.
    - Visual axis can become obstructed, leading to amblyopia.
- Allergic reactions
  - Contact dermatitis, insect bites, or bee stings can mimic preseptal cellulitis.
  - Differentiated by significant itching, limited pain, and boggy rather than tense edema.
- Hordeola and chalazia
  - Hordeola (sties) and chalazia are localized inflammatory reactions to blocked oil glands (meibomian glands) in the eyelid margin.
  - Focal areas of tense, firm, and often painful swelling with visible concretions in the oil glands near the areas of swelling.
- Blepharitis
  - Common, chronic inflammation and redness of the eyelid margin with blockage of the meibomian glands and associated crusting of the lashes
- Trauma
  - Often leads to edema and ecchymosis of the eyelids, making examination difficult
  - Lid speculum may be needed, if the physician is comfortable using this instrument.
  - If the eyelids cannot be opened with effort, retrobulbar hemorrhage should be suspected, and emergent ophthalmologic consultation should be obtained.
  - Avoid putting pressure on the eye until it is confirmed that the globe is intact.

Conjunctival Abnormalities

- Conjunctival redness
  - Can be focal or diffuse
  - Differential diagnosis includes
    - Viral or bacterial infection
    - Chemical exposure
    - Allergic reaction
    - Subconjunctival hemorrhage
    - Viral papilloma
    - Kawasaki disease
- See **Table 1.**
- Viral conjunctivitis.
  - Often highly contagious.
  - Complaints include
    - Itching
    - Burning or gritty sensation that typically starts in one eye and involves the second 2–5 days later
    - Watery discharge
    - Rhinorrhea
    - Sore throat
  - Patients sometimes recall recent exposure to a sick contact or someone with a red eye.
  - Often preauricular lymphadenopathy, and the conjunctiva often have follicles, or bumps of lymphoid aggregates best seen with fluorescein.
  - Severe cases sometimes have
    - Pseudomembranes of fibrin that cause scant bleeding when removed with cotton tips
    - Corneal subepithelial infiltrates, which are aggregates of immune cells
      - These occur 1–2 weeks after onset of symptoms and warrant referral to an ophthalmologist.
- Bacterial conjunctivitis.
  - Less common than viral conjunctivitis.
  - Often has a purulent rather than a watery discharge and a less follicular reaction.
  - Common bacteria include *Staphylococcus aureus, Staphylococcus epidermidis, Streptococcus pneumoniae*, and *Haemophilus influenzae.*
  - In teenagers, bacterial conjunctivitis can represent a sexually transmitted infection (STI), either gonorrhea or chlamydia.

Table 1. Differentiating Types of Conjunctivitis

	Bacterial	Viral	Allergic	Probable Referral
Presentation	Unilateral or bilateral	Usually unilateral, and then spreads to other eye	Usually bilateral; can be unilateral	
Season	Common in winter	Spring or fall	Spring or fall	
Onset	Concurrent with otitis media	Concurrent systemic viral infection	Acute or chronic	
Symptoms	Crusting on eyelashes Gluey or sticky eyelids ± fever	Tearing Eye irritation ± Fever	Itching Swelling of lids Conjunctival edema	Light sensitivity Pain Blurred vision
Discharge type	Purulent, thick, yellow/green	Serous or mucoid	Stringy, whitish ropy, if any	
Patient type	Younger children Contact lens wearer	Any age	>2 y	Red eye for ≥2 wk
Examination findings	Papules on conjunctiva	Follicles on palpebral conjunctiva Frequent preauricular nodes	Conjunctival edema and injection	

  - When STI is suspected, cultures should be taken, and the patient and sexual partners should be treated systemically for gonorrhea, usually with ceftriaxone.
  - Gonococcus.
    - Hyperacute onset and copious discharge.
    - Should be the first consideration because it can perforate a healthy cornea within 24 hours.
    - Infection usually manifests 3–4 days after birth.
  - Chlamydia.
    - Infection also can cause pneumonia and usually occurs within the first month of life.
    - Causes a chronic conjunctivitis with scant discharge and beefy inflammation.
    - Should be suspected when topical antibiotics fail to improve a bacterial conjunctivitis.
- Rarely, non-draining conjunctivitis can be caused by leptospirosis, tularemia, or toxin-mediated staphylococcal or streptococcal disease.

- Nasolacrimal duct obstruction.
  - Like bacterial conjunctivitis, can produce mucopurulent drainage, but conjunctiva typically remains white and non-inflamed.
  - Pressure over the nasolacrimal sac, inferior to the medial canthus, will cause reflux of watery mucoid discharge.
- Chemical conjunctivitis.
  - Exposure to a chemical irritant can produce rapid inflammation.
- Allergic conjunctivitis.
  - May be acute or chronic.
  - Almost always associated with itching.
  - Discharge may be clear with some mucus, or stringy and white.
  - Conjunctival edema with associated redness may appear as an intensely swollen eye.
- Vernal conjunctivitis.
  - A subset of allergic conjunctivitis that occurs most often in the springtime in young boys with a family history of allergies.
  - Often a ring of swollen, gelatinous conjunctiva with or without whitish-yellow deposits.
  - Papillae are common on the tarsal conjunctiva.

- Phlyctenulosis.
  - A subset of allergic conjunctivitis; a delayed hypersensitivity reaction that is often bilateral.
  - Results in a white, raised lesion on the conjunctiva or peripheral cornea, with dilated blood vessels at its borders.
  - Most common precipitant is exposure to staphylococci.
  - Also associated with tuberculosis or histoplasmosis.
- Subconjunctival hemorrhage.
  - Easily diagnosed by the often strikingly large patch of bright red on an otherwise white conjunctiva, usually in an asymptomatic patient.
  - Can occur after vaginal delivery, with Valsalva maneuver, with use of antiplatelet medications, from severe cough, or from trauma.
  - Non-accidental trauma should be considered in atypical cases.
  - Recurrence may suggest a bleeding disorder.
  - Resolves over 2–3 weeks without treatment.
  - It is worth counseling patients and parents that the lesion may expand slightly and change color as it resolves.
- Conjunctival papilloma.
  - Commonly a benign, self-limited lesion caused by human papillomavirus
  - Fleshy nodule with a sunburst vascular pattern
- Kawasaki disease.
  - Bilateral nonexudative conjunctivitis.
  - Acute vasculitis associated with fever, mucosal erythema, rash, cervical lymphadenopathy, and the potential for coronary artery aneurysms.
  - Conjunctivitis is usually self-limited.

Corneal Abnormalities

- Corneal abrasion/foreign body
  - Very painful presentation.
  - Complaints include
    - Foreign body sensation
    - Tearing
    - Often photophobia
  - Patients often recall a sudden onset after being hit or scratched in the eye.
  - Examination is often difficult, but instillation of anesthetic drops, such as proparacaine 0.5%, facilitates examination.
  - Abrasion is easily identified with a Wood lamp and fluorescein.
  - Foreign body should be suspected, and undersurface of the eyelids should be examined.
  - A corneal foreign body can be removed with a moist cotton-tipped applicator if superficial, but deeper ones should be referred to an ophthalmologist.
- Corneal ulcer
  - Caused by bacterial, fungal, viral, or parasitic organisms.
  - Contact lenses are a significant cause of corneal infections.
  - Sight-threatening condition that requires urgent ophthalmologic evaluation if there is corneal opacity, decreased vision, or ocular pain.
- Herpetic keratitis
  - Herpes simplex and varicella-zoster virus (VZV) can infect the eye.
    - VZV typically spreads to the eye from the face or eyelid.
    - Herpes simplex can infect the cornea directly.
  - Examination of the cornea with fluorescein reveals a dendritic branching epithelial defect.
  - If herpes is suspected, an ophthalmologic evaluation is urgently warranted to evaluate for intraocular involvement and intraocular pressure elevation.
  - Treatment of herpes simplex and VZV involves oral antivirals (acyclovir, valacyclovir) or topical antiviral eyedrops (trifluridine) or gel (ganciclovir).
  - If patients with a history of herpetic keratitis develop red eye, they should be seen by an ophthalmologist because recurrence is common.
  - Corneal herpes simplex disease often causes corneal scarring, which can be sight threatening.

Intraocular Abnormalities

- Corneal and ciliary flush is a violaceous, extreme engorgement of vessels at the corneal limbus that indicates involvement of deeper ocular structures.
  - Always refer to an ophthalmologist.
  - Differential diagnosis includes corneal infection, iritis, uveitis, and hyphema.
- Iritis/uveitis.
  - Inflammatory disorders within the eye often associated with sarcoidosis, herpes simplex, syphilis, tuberculosis, lupus, or autoimmune arthritides—including juvenile idiopathic arthritis (JIA) and the HLA-B27–positive spondyloarthropathies.
  - Photophobia, pain, and blurred vision.
  - Ciliary flush and a mid-dilated pupil usually present.

- With first episode of unilateral iritis, no workup is indicated because it will have an unidentified cause.
- However, with recurrent or bilateral disease, or with suspicion of a systemic disease, the underlying cause should be sought.
- In children with JIA, frequent screening for uveitis is critical.
  - Young patients with pauciarticular JIA should be evaluated every 3 months for 7 years.
  - Inflammation is commonly asymptomatic with few external findings.
  - Can lead to blindness if left untreated.

- Hyphema.
  - Blood collected in anterior chamber, behind the cornea and in front of the lens.
  - Almost exclusively a result of trauma, but in the absence of trauma suspect tumors and coagulopathies.
- Other inflammatory conditions include
  - Rare inflammatory conditions that cause focal conjunctival redness.
    - Scleritis
    - Episcleritis
    - Ocular myositis
  - Episcleritis has minimal discomfort, in sharp contrast to severe pain of scleritis.
  - The inflammation of myositis is seen overlying the affected extraocular muscle; patients often develop a head tilt to avoid using the sore muscle.
  - Workup for these conditions is the same as for recurrent iritis.

LABORATORY EVALUATION

- Iritis/uveitis
  - Antinuclear antibody, erythrocyte sedimentation rate, serum uric acid level, antineutrophil cytoplasmic antibody, rapid plasma reagin, and fluorescent treponemal antibody absorption
  - In children with JIA, frequent screening for uveitis
    - Young patients with pauciarticular JIA should be evaluated every 3 months for 7 years
- Mild to moderate preseptal cellulitis
  - Laboratory evaluation is not usually needed.
- For orbital cellulitis, highly febrile patients or severe preseptal cellulitis
  - Complete blood cell count and blood culture
- Chlamydia and gonococcus
  - Cultures should be taken with special media.

IMAGING

- Preseptal cellulitis
  - Computed tomography (CT) with contrast of orbits and sinuses provides details related to bony structures or radiopaque foreign bodies.
    - Should be performed in significant trauma or suspected foreign body, sinus disease, suspected orbital involvement, or abscess formation.
- Orbital cellulitis
  - CT of the orbits and sinuses with and without contrast to evaluate for foreign bodies, sinus disease, and abscess formation
  - Orbital tumors, such as neuroblastoma, rhabdomyosarcoma, and lymphangioma, can masquerade as orbital cellulitis.
    - Magnetic resonance imaging may provide better delineation of soft tissue details, particularly if intracranial complication is suspected.

SPECIFIC TREATMENT

- Blepharitis
  - Lid scrubs using nonirritating products such as baby wash or baby shampoo to remove crusting
  - Warm soaks to help drain the meibomian glands
  - Antibiotic ointment to the lids to reduce the bacterial load on the skin
- Viral conjunctivitis
  - Treatment is supportive, with a focus on minimizing contagion.
  - Patients and parents should be instructed to wash their hands often and not share towels or bed linens.
  - For symptomatic relief in nonspecific viral conjunctivitis or adenovirus
    - Chilled preservative-free artificial tears 4–8 times a day
    - Cool compresses several times a day
  - In group care settings, if 2 or more children are infected with conjunctivitis at the same time, it is appropriate to seek the advice of a health care professional or department of health.
  - Treatment of herpes simplex and VZV involves
    - Oral antivirals (acyclovir, valacyclovir) *or*
    - Topical antiviral eyedrops (trifluridine) or gel (ganciclovir)
- Bacterial conjunctivitis
  - Topical antibiotic treatment is often successful.
  - Drops (trimethoprim-polymyxin B, moxifloxacin, or gentamicin 4 times a day for 7–10 days) *or*

- Ointment (bacitracin-polymyxin B or erythromycin 4 times a day for 5–7 days).
- *Neisseria gonorrhoeae* is treated with intravenous (IV) ceftriaxone.
- Chlamydia treatment of patient and contacts is with oral azithromycin or doxycycline.
  - Doxycycline should be avoided in children <8 years because of possible permanent tooth staining.
- Chemical conjunctivitis.
  - For exposure to household chemicals, the most important treatment is immediate and copious irrigation with the nearest source of water.
    - Check pH of the conjunctival surface (basic solutions penetrate deeper and cause more damage than acids).
    - Irrigation should continue until pH remains 7.0 for several minutes after an interruption.
  - In most cases, however, artificial tears and topical antibiotic eyedrops are sufficient.
- Allergic conjunctivitis.
  - Cool compresses, topical antihistamines and mast cell stabilizers, oral antihistamines, topical steroids, and, rarely, oral steroids
- Phlyctenulosis.
  - Treatment is the same as for blepharitis, with addition of interventions to treat the allergic component.
  - Patients with significant irritation may require topical steroids and should be referred.
- Conjunctival papilloma.
  - For large, multiple, recurrent, or cosmetically disturbing lesions, treatment options include cryotherapy, surgical excision, and oral cimetidine.
- Kawasaki disease conjunctivitis.
  - Can be treated with artificial tears
- Iritis/uveitis.
  - In JIA, treatment includes topical or oral steroids to control the disease and cycloplegia to prevent iris adhesions and reduce photophobia.
  - In long-term steroid use, intraocular pressure should be monitored.
- Episcleritis.
  - Oral nonsteroidal anti-inflammatory drugs (eg, ibuprofen) alone or accompanied by topical steroids
- Hyphema.
  - Cycloplegia to prevent iris movement and adhesions
  - Topical steroids to decrease inflammation
  - Reduced patient activity to prevent a rebleed

WHEN TO REFER

- Ophthalmology referral is appropriate for
  - Red eye associated with pain, photophobia, or blurry vision
  - Severe conjunctivitis
  - Conjunctivitis associated with contact lens use
  - Chronic conjunctivitis that does not improve after 7 days of treatment
  - Herpes simplex conjunctivitis, for a more complete examination to evaluate for intraocular involvement and pressure elevation, and antiviral therapy
  - Patients with a history of herpetic keratitis who develop red eye because recurrence is common
    - Herpes keratitis often causes corneal scarring, which can threaten vision.
  - Chemical conjunctivitis with areas of white clear conjunctiva or corneal clouding suggesting necrosis
    - Refer urgently for aggressive treatment.
  - Eyelid tumor caused by capillary hemangiomas and port-wine stain of Sturge-Weber syndrome
  - Hordeola and chalazia if not resolved in 4–6 weeks, or if there is significant worsening
    - Refer for evaluation of possible surgical drainage.
  - Corneal ulcer caused by bacterial, fungal, viral, or parasitic organisms
    - Urgent evaluation if there is corneal opacity, decreased vision, or ocular pain
  - Suspected herpes to evaluate for intraocular involvement and intraocular pressure elevation
  - Hyphema for monitoring of intraocular pressure during treatment

WHEN TO ADMIT

- Orbital cellulitis
  - For IV antibiotics and possible surgical drainage
- Suspicion of an orbital tumor
- Trauma with orbital disruption

DEFINITION

- Renal tubular acidosis (RTA) is impaired capacity of the kidney to excrete the usual daily load of acid arising from metabolism.
  - Renal excretory function, as estimated by creatinine clearance, is relatively intact.
  - Metabolic acidosis results from a defect affecting tubular mechanisms for acid excretion.
  - Not caused by under-excretion of acid due to kidney failure or increase in acid production (ie, in diabetic ketoacidosis, lactic acidosis, or total parenteral nutrition).
- Consequence of mismatch between the usual rate of acid production and renal acid excretion.
- Not a single entity but, rather, a collection of complex disorders.
- Principal cause of hyperchloremic metabolic acidosis with normal anion gap in an infant or child ingesting a typical diet who does not have gastroenteritis or chronic kidney disease.

SIGNS AND SYMPTOMS

- Failure to thrive during infancy is often a presenting feature of RTA.
- Rarely presents as isolated idiopathic hypercalciuria or passage of a kidney stone in a child with incomplete RTA.
  - Which may be accompanied by a family history of nephrolithiasis in association with hypocitraturia
- For some children in at-risk families, hypocitraturia may be the only indication of impaired urinary acidification with normal plasma bicarbonate (incomplete RTA).
- Family history should be explored with questions about other affected family members in preceding generations or affected siblings of the individual with suspected RTA.
- With apparent de novo RTA, consanguinity may play a role.
- Nephrolithiasis in other family members may be significant.
- A history of sudden unexplained death in a neonate suggests the possibility of a salt-losing condition that may be associated with RTA.

DIFFERENTIAL DIAGNOSIS

- The clinician is more likely to encounter secondary forms of RTA that result from drugs, toxins, or acquired medullary tubulointerstitial disease.
  - **Table 1** lists drugs associated with RTA.
- Other instances of RTA are associated with
  - Another heredofamilial disorder, such as cystinosis, *or*
  - Other causes of Fanconi syndrome
- The transient form of RTA may occur in young infants with delayed maturity of renal tubular function.

Table 1. Drugs Associated With Acquired Renal Tubular Acidosis

Reclamation-Type RTA	Regeneration-Type RTA	Hyperkalemic Regeneration-Type RTA	Hybrid
Acetazolamide	Amiloride	Spironolactone	Acetazolamide
Sulfanilamide	Trimethoprim	Eplerenone	Sulfonamide
Topiramate	Trimethoprim-sulfamethoxazole	ACE inhibitor	Topiramate
Valproic acid	Tacrolimus	Angiotensin-receptor blocker	
Methotrexate	Amphotericin B		
Date-expired tetracyclines	Lithium		
6-mercaptopurine	Analgesic abuse		
Outdated aminoglycoside	Vitamin D overdose		
Mafenide acetate	Foscarnet		
Cisplatin	Methicillin		
Antiretroviral			

Abbreviations: ACE, angiotensin-converting enzyme; RTA, renal tubular acidosis.

- RTA, in association with hyponatremia and hyperkalemia, can present as an acute life-threatening event in some infants with profound salt-losing condition and hypovolemia.
  - Pseudohypoaldosteronism type 1
  - Congenital adrenal hyperplasia with insufficient mineralocorticoid production
- Reclamation-type RTA may be an isolated defect and, in some infants, simply a transient immaturity of function that eventually resolves.
- Heredofamilial RTA syndromes in children occur because of mutations of genes encoding ion transporters that play a key role in the kidney's contribution to acid-base homeostasis.
  - Rare primary monogenic disorders that usually have autosomal-recessive mode of inheritance and may be associated with ocular defects or hearing impairment.
  - Pseudohypoaldosteronism type 1.
  - Salt-losing congenital adrenal hyperplasia.
  - These are not "classic" RTA but, rather, metabolic acidosis as a secondary accompaniment of impaired mineralocorticoid receptor function or aldosterone deficiency.

DIAGNOSTIC APPROACH

- RTA should be considered in any infant or young child with metabolic acidosis accompanying any of the following conditions:
  - Failure to thrive
  - Recurrent vomiting
  - Short stature
  - Rickets
  - Nephrocalcinosis
  - Hypotonia
  - Muscle weakness
  - Sensorineural hearing loss
  - Recurrent episodes of dehydration
  - Kidney stones
  - Gastroenteritis with incomplete recovery from metabolic acidosis
  - Family member known to have RTA

LABORATORY FINDINGS

- In the absence of blood gas analysis confirming acidemia, consider RTA if
  - Venous blood carbon dioxide (CO_2) content is <20 mEq/L in an infant or young child with failure to thrive in the absence of diarrhea and
    - The child has hyperchloremia.
    - The anion gap is normal.
    - Urine pH is ≥5.5.
- Once a renal cause for hyperchloremic metabolic acidosis is established, estimate urinary ammonium (NH_4^+) by measuring Na^+, K^+, and Cl^- in a random urine specimen and calculating the urinary anion gap (UAG): $UAG = Na^+ + K^+ - Cl^-$.
  - On a typical diet, Cl^- is the main anion accompanying urinary NH_4^+, and the concentration of Cl^- exceeds the sum of the concentrations of Na^+ and K^+.
  - Because urinary NH_4^+ is not directly measured, the UAG is negative or close to 0 in healthy persons.
  - With regeneration-type RTA, the rates of NH_4^+ excretion and Cl^- excretion are low and concentration is usually less than the sum of $Na^+ + K^+$ in the formula; in this instance, UAG is positive.
  - This estimate is less reliable if urine pH is relatively alkaline, >6.7, at which HCO_3^- becomes a significant component of unmeasured anions.
  - UAG is normal in reclamation-type RTA during the acidemia that ensues after stopping alkali treatment.
    - UAG estimate in such patients is not reliable during alkali treatment because of massive HCO_3^- wasting.
    - The reliability of this estimate is negatively affected by an increase in other unmeasured anions (eg, keto acid anions, sulfate; the latter may be a consequence of a high protein intake).
- Urine osmolal gap (UOG): another surrogate measure for urinary NH_4^+.
  - $UOG = (\text{measured urine osm}) - (2[Na_u^+ K_u^+] + [urea_u] + [glucose_u])$
  - Actual NH_4^+ is approximately half the UOG because concentrations of NH_4^+ and Cl^- are approximately equal.
- If serum K^+ concentration is low or normal, diagnostic possibilities include reclamation-type or non-hyperkalemic regeneration-type RTA.
- If urine glucose is positive, further testing is done to establish Fanconi syndrome in association with reclamation defect.
- Empiric treatment with citrate solution may confirm diagnosis of reclamation defect if dose required to correct the serum HCO_3^- approaches 10–15 mEq/kg/d.
  - An increased dose may be required in some infants with regeneration-type RTA as a transient phenomenon during the first few years of life.

- Ammonium chloride challenge to assess the ability to maximally acidify urine.
  - Rarely performed in children.
  - The (U – B) PCO_2 difference may indicate a limitation of acidification if the (U – B) PCO_2 is <20 mm Hg, consistent with a defect of the apical H^+–adenosine triphosphatase of the type A intercalated RTA and should only be performed after treatment with alkali has restored plasma HCO_3^- level to normal.
  - It is best done under the supervision of a nephrologist in collaboration with a laboratory able to process urine collected under mineral oil to prevent loss of CO_2.
    - Not readily accomplished in a young child who is not yet toilet trained unless single-pass catheterization is done
  - Acidification may also be assessed by giving a challenge dose of furosemide, 1 or 2 mg/kg, following administration of a priming dose of fludrocortisone (0.1 mg) several hours earlier.
  - Intact acidification is indicated by urine pH <5.5.
- In young infants, obtaining reliable 24-hour urine collection to estimate calcium excretion is impossible without an indwelling catheter.
  - Collect multiple random "bag" specimens throughout the day to estimate the urine calcium to creatinine ratio.
- Age range and calcium to creatinine ratio (mol/mol, mg/mg), 95th percentiles.
  - 1 month–1 year: 2.2, 0.81
  - 1–2 years: 1.5, 0.56
  - 2–3 years: 1.4, 0.50
  - 3–5 years: 1.1, 0.41
  - 5–7 years: 0.8, 0.30
  - 7–10 years: 0.7, 0.25
- If the serum K^+ concentration is high, suggesting hyperkalemic regeneration-type RTA, an impaired capacity to secrete K^+ may be confirmed by
  - Measurement of K^+ and osmolality in plasma
  - Random urine specimen obtained at the same time that blood is sampled
  - Calculation of the trans-tubular potassium gradient (TTKG)
    - In the setting of hyperkalemia, TTKG should be ≥8 if the collecting duct responds to mineralocorticoid.
    - A value <8 suggests insufficient production of aldosterone or lack of responsiveness of the mineralocorticoid receptor aldosterone.
- Pseudohypoaldosteronism type 1 is suggested by increased level of plasma aldosterone and plasma renin.
- If aldosterone and renin are suppressed and blood pressure is increased, the rare familial hyperkalemic hypertension syndrome (pseudohypoaldosteronism type 2) is possible.
- If blood pressure is normal or low and aldosterone is low in clinical setting of salt-wasting, consider congenital adrenal hyperplasia.
- If aldosterone is high, consider the severe, potentially fatal neonatal presentation of pseudohypoaldosteronism type 1.
- Salt-losing congenital adrenal hyperplasia.
  - If suspected, initial testing should include plasma cortisol, aldosterone, and 17-hydroxyprogesterone.
  - The salt-losing tendency is ameliorated by fludrocortisone in conjunction with cortisol replacement.
  - The metabolic acidosis is usually not severe, and further management is best performed by a pediatric endocrinologist.

IMAGING

- Ultrasonography
  - Medullary nephrocalcinosis confirms non-hyperkalemic regeneration-type RTA because this type is also associated with hypercalciuria and hypocitraturia.

CLASSIFICATION

- Physiologic classification: now in use because it is physiologically accurate (**Table 2**)

TREATMENT APPROACH

- Aims of treatment include
  - Correct metabolic acidosis.
  - Correct growth impairment.
  - Mitigate osteopenia.
  - Prevent chronic kidney failure caused by progression of nephrocalcinosis (in the instance of a primary H^+ secretory defect [regeneration defect]).
- Appropriate treatment with alkali restores growth to the expected trajectory, but the requirement to sustain growth was 2- to 5-fold greater than the expected rate of endogenous acid production.
  - Alkali in this context refers to sodium bicarbonate or a bicarbonate precursor, such as sodium or potassium citrate.

Table 2. Classifications of Renal Tubular Acidosis

Physiologic	Conventional
Reclamation defect	Type 2, proximal
• With Fanconi syndrome • Primary, nonsyndromic	
Regeneration defect	Type 1, distal
• Non-hyperkalemic	
• Hyperkalemic — Acidification intact ■ Pseudohypoaldosteronism types 1a, 1b, 2 — Acidification impaired ■ Medullary tubulointerstitial disease	Type 4
Hybrid	Old type 3

SPECIFIC TREATMENTS

Citrate Solution

- Mainstay of treatment in most children.
- Hypokalemia and K^+ depletion are characteristic of non-hyperkalemic regeneration-type RTA; thus, potassium citrate preparation is optimal.
- The usual liquid preparation contains
  - 2 mEq/mL of K^+ and 2 mEq/mL of HCO_3^- precursor as citrate.
  - Citric acid (to make it palatable).
  - pH ~5 before further dilution.
  - Solution is hyperosmolar; must first be diluted 4- or 5-fold with water or infant formula before oral administration.
- Potassium citrate is available for older children as a capsule in 2 forms, providing 5 mEq or 10 mEq of K^+.
  - Slowly released from wax matrix; the capsule must be swallowed whole and not opened or crushed.
  - A combined sodium and potassium citrate solution provides 1 mEq of K^+/mL and 1 mEq of Na^+/mL and also requires dilution before administration.
  - Potassium-containing solutions must be avoided in hyperkalemic forms of RTA.
- Monitor serum potassium, especially if the glomerular filtration rate is reduced or the patient is receiving angiotensin-converting enzyme inhibitor or angiotensin-receptor blocker.
- Sodium citrate–containing solutions (1 mEq/mL)
  - May be used for buffer repletion in hyperkalemic regeneration-type RTA.
  - These solutions provide 1 mEq of Na^+/mL and, thus, have lower osmolality than sodium and potassium citrate solution (2 mEq/mL) or potassium citrate solution (2 mEq/mL).
  - Requires dilution to lower strength for safety and palatability.
  - Total daily dose should be divided into 3 or 4 doses to minimize amplitude of fluctuations of serum HCO_3^- level that may occur with less frequent administration.
  - Metabolic acidosis inhibits growth hormone secretion, so administer a somewhat larger dose of citrate solution at bedtime to coincide with the nocturnal peak of growth hormone release.
  - Citrate accomplishes 2 aims.
    - — Inhibition of stone formation by complexing ionic calcium in urine and as a bicarbonate precursor, correction of metabolic acidosis.
    - — However, citrate can raise the risk of calcium phosphate stone formation.
      - ■ This may be monitored by periodic assessment of the supersaturation index of calcium.
- Baking soda powder ($NaHCO_3$) may be used, but rapid buildup of CO_2 in the stomach after ingestion may cause gastric distention.
  - This approach may be a preferable means of buffer repletion in infants who refuse citrate solutions.
  - One-quarter teaspoon of $NaHCO_3$ provides 13 mEq each of Na^+ and HCO_3^- and should be diluted in water or infant formula.
  - Tablets of $NaHCO_3$ are available, which may be crushed.

- Adequate treatment of non-hyperkalemic RTA with citrate should lessen hypercalciuria.
  - Nephrocalcinosis, once established, is not reversible.
  - The aim of treatment is to prevent its further progression to end-stage kidney disease.
- Correction of acidosis in patients with regeneration-type RTA does not ameliorate hearing impairment associated with the 2 autosomal-recessive forms of proton-pump defects.
- Diet.
  - Dietary intake emphasizing meat is acidogenic.
  - Intake of fruits and vegetables should be encouraged because some of these are also sources of potassium and citrate.
- Monitor growth and serum electrolytes periodically.
  - Maintain serum HCO_3^- near the upper limit of range 25–29 mEq/L.
  - Draw blood just before the next dose of alkali.
  - At these levels of HCO_3^-, osteoclastic bone resorption may be suppressed sufficiently to lower the risk of long term osteopenia or osteoporosis.

WHEN TO ADMIT

- Hypovolemia (often caused by an illness accompanied by diarrhea or vomiting).
- Hypokalemia with serum K^+ <2.5 mEq/L, especially if accompanied by muscle weakness.
- If adherence to the medication regimen or intercurrent illness interferes with taking medication, hospitalization may be needed for parenteral administration of HCO_3^-.
- Kidney stone.

WHEN TO REFER

- RTA is suspected by assessment of UAG or UOG or suggested by family history.
- Fanconi syndrome is suspected.
- Comprehensive evaluation of suspected RTA entails studies in a kidney function laboratory; referral to a nephrologist is appropriate.
- The role of the primary care physician is to
  - Be aware of the possibility of RTA.
  - Take initial steps in patient's workup, such as calculation of UAG or UOG.
- More detailed studies and explanations to parents are best accomplished by a pediatric kidney disease specialist.
- Genetic counseling is needed for parents with a child who has monogenic RTA disorder, in anticipation of possible future pregnancies.
- Because commercially available gene testing is not yet available, the consultant nephrologist may have access to a research laboratory capable of sequencing DNA.

FOLLOW-UP

- Once a child is established on an effective treatment regimen and is clinically stable with good growth progress, periodic follow-up by the primary care physician may be done in collaboration with a nephrologist.

COMPLICATIONS

- RTA associated with episodic hypokalemia may be accompanied by profound muscle weakness and, in some instances, recurrent paralysis.
- Most children with RTA (especially those with nephrocalcinosis) have impairment of urinary concentrating mechanism and consequent obligatory polyuria.
- Superimposed dehydrating illness (eg, diarrhea, protracted vomiting) can culminate in profound hypovolemia.
  - This susceptibility warrants prompt hospitalization and fluid administration before signs of severe dehydration emerge.
- Susceptibility to hypokalemia in children with regeneration-type RTA calls for regular monitoring of serum K^+.
  - If low, increase dose of potassium-containing citrate solution.
  - If profound hypokalemia exists with a serum K^+ concentration <2.5 mEq/L accompanied by muscle weakness, prompt hospitalization may be needed.
- Newborns with salt-losing tendency should be monitored closely.
  - If the disorder was not recognized before discharge from nursery, the following signs call for urgent readmission and vigorous volume repletion:
    - Emergence of vomiting
    - Feeding difficulty
    - Listlessness
    - Hypotonia
    - Hyperventilation
    - Pallor
    - Signs of dehydration

- In the absence of virilization, congenital adrenal hyperplasia in a male neonate may not be recognized at birth.
  - Neonate may be discharged from nursery only to develop profound salt-wasting and hypovolemic shock 1–2 weeks later.

DEFINITION

- Acute rheumatic fever is a systemic connective tissue disorder characterized by polyarthritis, carditis, and chorea (singly or in combination).

SIGNS AND SYMPTOMS

Major Clinical Manifestations

- The sequence of manifestations of rheumatic fever
  - Polyarthritis, when it occurs, is usually present before onset of carditis.
  - Carditis may be present without preceding joint symptoms.
    - — Most often, apical systolic murmur of mitral valvulitis occurs ≤2 weeks of onset of arthritis.
  - Diastolic murmur of isolated aortic valvulitis takes longer to appear.
    - — May not be heard for 6–8 weeks after joint signs and symptoms appear
  - Chorea may develop during the convalescent phase of carditis.
    - — A longer latent period usually occurs.
    - — Classically, chorea appears as an independent manifestation long after initial streptococcal infection.
    - — Most cases begin 2 months after streptococcal infection, with episodes occurring ≤6 months afterward.
  - Chorea and carditis may coexist.
  - Chorea and polyarthritis rarely appear concurrently, presumably because of the difference in latent periods.

Polyarthritis

- Most common manifestation at the onset of rheumatic fever.
  - Usually involves large joints of lower extremities, particularly ankles or knees
- May result in joint pain while walking.
  - Often initially considered to be secondary to trauma
- Other large joints become involved in a migratory fashion (eg, wrists and elbows).
- The affected joint characteristically is
  - Warm
  - Reddened
  - Minimally swollen
- Involved joints are
  - Exquisitely sensitive to touch
  - Painful on motion
- Suggestive of, but not specific for, rheumatic fever.
  - Arthralgias, or aching in joints without objective signs of inflammation
- Fever is almost always present.

Carditis

- Inflammation of cardiac tissue, characteristically expressed as valvulitis.
  - Pancarditis involving myocardium and pericardium in severe cases
- Murmurs audible in rheumatic carditis are the result of mitral or aortic valvulitis, or both.
  - Mitral involvement is, by far, the most common.
- Auscultatory diagnosis of valvulitis often includes presence of an apical mid-diastolic murmur.
- May include pericarditis.
  - Typically silent.
  - Occasionally, friction rub or distant heart sounds.
  - Isolated pericarditis without associated auscultatory findings of mitral or aortic involvement is not consistent with diagnosis of acute rheumatic fever.
- The differential diagnosis of myocarditis and pericarditis include viral inflammation of the heart by coxsackievirus type B and Kawasaki disease.
  - These do not cause valvulitis.
- Auscultation of heart and evaluation of murmurs are influenced by fever and tachycardia.
  - The patient should be reexamined frequently after
    - — Diagnosis of acute rheumatic fever
    - — Normalization of temperature with aspirin therapy
  - A changing functional murmur in an anxious or febrile child does not indicate carditis.
- Carditis is clinically diagnosed by the presence of valvulitis with characteristic murmurs.
  - May be designated as mild, moderate, or severe
  - Such categorization is useful in
    - — Approach to management
    - — Establishing prognosis
- Mild carditis.
  - Characteristically defined by prominent, high-pitched, apical systolic murmur typical of mitral insufficiency.
  - Heart murmur of mild carditis is usually of grade 2 or 3 intensity (on a scale of 1–6).
    - — Occupies all or most of systole
  - Mid-diastolic rumble at the apex is not present.

- Moderate carditis.
  - Defined as
    - Long systolic and prominent mid-diastolic apical murmurs, reflecting greater severity of mitral valvulitis
    - Basilar diastolic murmur of aortic valvulitis
    - Combination of mitral and aortic valvulitis
  - Aortic diastolic murmur
    - High pitched, decrescendo in character
    - Heard best during end expiration with diaphragm of stethoscope placed firmly at the third left intercostal space
- Severe carditis.
  - Defined by the presence of
    - Pericarditis
    - Congestive heart failure
    - Mitral or aortic valvulitis
  - Quality of heart sounds may be poor because of
    - Pericardial effusion
    - Low cardiac output
  - Murmurs may become more intense as cardiac compensation improves.
- Subclinical carditis.
  - Patients who have no clinical evidence of carditis.
  - Echocardiography and Doppler testing should be performed in any patient suspected of having rheumatic fever, even in the absence of clinical findings of cardiac disease.
  - Strict echo/Doppler criteria should be followed to diagnose active subclinical carditis, which includes changes in the mitral or aortic valve and documented pathologic mitral or aortic regurgitation.

Chorea

- Clinical picture of Sydenham chorea.
  - Includes poor neuromuscular coordination.
  - Sometimes first detected by a change or sloppiness in handwriting.
  - May also include jerky, involuntary movements.
    - Lasts 6–8 weeks when most cases of chorea are active.
  - Neurologic examination may give evidence of specific deficiencies, particularly in the trunk and upper extremity control of movements.
- When chorea occurs as an isolated manifestation, the patient is usually afebrile.
  - The sedimentation rate is normal.
  - Long interval after the initiating streptococcal infection.
    - Antistreptolysin O (ASLO) titer is typically normal or only mildly elevated.
  - Murmur of mild mitral insufficiency may be noted.

Erythema Marginatum

- Transient pink rash with irregular, deeper-colored serpiginous borders
  - Seen on the smooth, hairless surfaces of the inner aspect of the upper arms and thighs or trunk
- Infrequently encountered in recent decades

Subcutaneous Nodules

- Characteristically pea sized.
- Usually located on the extensor surfaces of
  - Fingers
  - Toes
  - Elbows
  - Other joints
  - Occiput (less frequently)
- Usually reflect long-standing or smoldering illness after severe carditis.
- Nodules may persist for weeks or months.
- Subcutaneous nodules are now rarely found in children with rheumatic fever.

Minor Clinical Manifestations

- Nonspecific fever.
- Nonspecific arthralgia.
  - Defined as joint discomfort without objective signs of inflammation
- Elevated acute-phase reactant, such as erythrocyte sedimentation rate (ESR), 60–120 mm/h initially.
  - In chorea, the sedimentation rate is normal due to long interval beyond the antecedent streptococcal infection.
- C-reactive protein (CRP) is elevated in a variety of other diseases.
  - Helpful in diagnosing cases with borderline findings
- The minor criteria have also been modified to differentiate low-risk versus moderate-risk and high-risk populations.
  - Minor criteria in the low-risk group include polyarthralgia, fever >38.5°C (101.3°F), and ESR >60 mm/h.
  - Moderate-risk and high-risk group minor criteria have been changed to include monoarthralgia, fever >38.0°C (100.4°F), and ESR >30 mm/h.
  - CRP >3.0 mg/L and a prolonged PR interval remain the same in both groups.

- Streptococcal pharyngitis presumptively precedes an attack of rheumatic fever.
  - Some patients fail to report such a history.
- Scarlet fever is occasionally followed by signs of polyarthritis or carditis.
  - Suppurative streptococcal disease, such as skin infection, is not a precursor of rheumatic fever.
  - Polyarthritis and carditis usually occur 3–5 weeks after infection.
- ASLO titer peaks before onset of clinical symptoms, and then decreases gradually.
- Occasionally, children have abdominal pain after streptococcal infection for which medical or surgical evaluation is sought.
  - May occasionally precede signs of joint or cardiac involvement.

DIFFERENTIAL DIAGNOSIS

- Throat cultures may be misleading.
  - Streptococcal infection antedates common manifestations of polyarthritis and carditis by 3–8 weeks.
  - ≤50% of patients with rheumatic fever continue to harbor streptococci during the course of their illness.

DIAGNOSTIC APPROACH

- No pathognomonic clinical findings and specific laboratory tests are available.
  - Diagnosis must be somewhat arbitrary and empirical.
  - Avoid the tendency to label any low-grade febrile illness with arthralgia for which no obvious cause can be found as rheumatic fever.
- Major and minor criteria for evaluation and diagnosis of rheumatic fever and rheumatic heart disease by Dr T. Duckett Jones (**Table 1**).
  - Final diagnosis remains a clinical judgment; Jones criteria should be viewed as a guide to a probable diagnosis of rheumatic fever.
  - Evidence of antecedent group A streptococcal (GAS) infections, 2 major manifestations, or 1 major and 2 minor manifestations indicates high probability of acute rheumatic fever.
  - A recent review of the Jones criteria was published in 2015, with the following highlights:
    - Proposing different criteria for medium-risk and high-risk versus low-risk populations.
    - Use of Doppler echocardiography in the diagnosis of silent carditis.
    - Including monoarticular arthritis as a major criterion in moderate-risk and high-risk populations.
    - *Low risk* is defined as having an incidence of acute rheumatic fever of <2 per 100,000 school-aged children per year or an all-age prevalence of rheumatic heart disease of ≤1 per 1,000 population per year.
- Poststreptococcal reactive arthritis (PSRA) may complicate the diagnosis of acute rheumatic fever.
  - PSRA refers to patients who have arthritis following GAS pharyngitis without other criteria for rheumatic fever.
  - It is unclear whether PSRA is a distinct syndrome or if antibiotic prophylaxis is required.
- Minor manifestations.
  - Elevated acute-phase reactants: ESR and CRP level
  - Electrocardiographic (ECG) evidence of prolongation of the PR interval
- Fever may be present early in the course of polyarthritis or carditis.
- Arthralgia.
  - A minor manifestation
  - Nonspecific
  - May affect any joint without objective signs of inflammation
  - Should not be considered a minor manifestation if arthritis is counted as a major manifestation
- False diagnosis of acute rheumatic fever results in unnecessary long-term antibiotic prophylaxis and should be avoided.

LABORATORY FINDINGS

- Under current guidelines, laboratory confirmation of recent streptococcal infection should be part of the diagnostic evaluation.
  - Absence of evidence should make the clinician suspicious of the diagnosis of rheumatic fever.
  - Exception: cases in which indolent carditis or chorea are the major manifestations.
- Minor clinical manifestations.
  - Elevated acute-phase reactant is an invaluable, though nonspecific, sign of inflammation.
    - ESR
- Most reliable evidence of a preceding streptococcal infection.
  - Obtained by demonstration of antibody response to ≥1 of the streptococcal antigens.
  - ASLO titer.
    - Most common.
    - Reaches maximal levels 3–5 weeks after infection.

Table 1. Revised Jones Criteria for the Diagnosis of an Initial Episode of Rheumatic Fever

Low-risk Populations	Moderate-risk and High-risk Populations
Major Criteria	
Carditis	Carditis
• Clinical or subclinical	• Clinical or subclinical
Arthritis	Arthritis
• Polyarthritis only	• Monoarthritis or polyarthritis
• Chorea	• Polyarthralgia
Erythema marginatum	Chorea
Subcutaneous nodules	Erythema marginatum
	Subcutaneous nodules
Minor Criteria	
Clinical findings	
Polyarthralgia	Monoarthralgia
Fever (≥38.5°C [101.3°F])	Fever (>38.5°C [101.3°F])
Laboratory findings	
ESR ≥60 mm/h	ESR ≥30 mm/h
CRP ≥3.0 mg/L	CRP ≥3.0 mg/L
Prolonged PR interval	Prolonged PR interval
Supporting Evidence of Antecedent GAS Infections	
• Positive throat culture or rapid streptococcal antigen test result	
• Elevated or rising streptococcal antibody titer	

Abbreviations: CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; GAS, group A streptococcus.

From Gewitz MH, Baltimore RS, Tani LY, et al. Revision of the Jones Criteria for the diagnosis of acute rheumatic fever in the era of Doppler echocardiography: a scientific statement from the American Heart Association. *Circulation*. 2015;131(20):1806–1818. Reprinted with permission.

R

  - Gradually declines to preinfection levels 6–12 months later.
  - Elevated in ~85% of patients with rheumatic fever.
  - Titers are never extremely low.
- Serologic evidence of an antecedent streptococcal infection increases to 95% if other streptococcal antibody tests are performed.
  - Anti-hyaluronidase
  - Anti-deoxyribonuclease B
  - Antistreptokinase

IMAGING

- Cardiac ultrasonography
  - 2-dimensional echocardiography for documentation and quantification of pericardial effusion.
  - Interpretation of valvular regurgitation by Doppler ultrasonography should not constitute the basis of a diagnosis of carditis.
  - Doppler studies in healthy individuals frequently show a small degree of regurgitation across the mitral valve.
  - Trivial aortic valve regurgitation may be noted occasionally.

- Strict Doppler and echocardiographic criteria are available in the American Heart Association (AHA) guidelines to differentiate valvular disease typical of rheumatic carditis from normal variants.
- Several recent studies have assessed 2-dimensional echocardiography as a screening tool to identify children with a past history of unsuspected rheumatic carditis.
- It is important to distinguish the use of echocardiography in areas with a high incidence of endemic rheumatic fever from its use in areas of low incidence.

■ Chest radiography
- In mild carditis, heart size is usually normal.
- In moderate carditis, may show mild cardiac enlargement.
- In severe carditis, shows obvious cardiomegaly.
  - — May reveal pulmonary vascular congestion compatible with left-sided heart failure and pulmonary edema.
  - — Appearance may be consistent with rheumatic pneumonia.

DIAGNOSTIC PROCEDURES

■ ECG of minor clinical manifestations.
- Prolongation of the PR interval (first-degree heart block) on ECG is considered to be a vagal effect and supports the diagnosis of rheumatic fever.
  - — Most commonly noted when polyarthritis is apparent
  - — Not necessarily associated with carditis
- ECG is almost always otherwise normal regardless of cardiac involvement.

■ ECG may demonstrate PR interval prolongation.
- Occasionally, second- or third-degree heart block occurs.
- Indicates further heightening of vagal tone.
- Perhaps more pronounced in the rheumatic state than in other acute illnesses.

■ ECG demonstrating first- or second-degree heart block is not common.
- Major criterion for carditis
- Harbinger of potential rheumatic heart disease
- Threat to progress to complete heart block

TREATMENT APPROACH

■ Therapeutic management of acute rheumatic fever includes the use of
- Antistreptococcal antibiotics
- Anti-inflammatory agents

SPECIFIC TREATMENTS

Chorea

■ A protective environment is recommended while the process is active.
■ Occasionally, mild sedation is indicated.
■ Agents that may help in the treatment of more severe movement disorders include
- Valproic acid
- Prednisone

Antistreptococcal Therapy

■ Eradication of GAS infection with antibiotics is the foremost principle in management of acute rheumatic fever.
- Even in the absence of a positive throat culture result

■ Antibiotic treatment must always be immediately followed by a prophylaxis to prevent reinfection.
■ Penicillin is the drug of choice, prescribed initially at a dose and duration to maintain therapeutic blood levels for 10 days.
■ Several treatment schedules are outlined by the AHA.
- Intramuscular administration of long-acting repository benzathine penicillin G (Bicillin) is preferred at time of diagnosis.
  - — Ensures therapeutic levels for a sufficient length of time
  - — A single injection of 1.2 million units for children 5–15 years of age
- Alternative methods.
  - — Oral penicillin, 200,000 or 250,000 units (penicillin G or penicillin V), given 3 or 4 times a day for a full 10 days *or*
  - — Combination of oral and intramuscular penicillin
- For patients sensitive to penicillin, erythromycin may be used for antistreptococcal therapy.
- Sulfonamide drugs are not effective for streptococcal eradication.
  - — Bacteriostatic rather than bactericidal
  - — Can be used to prevent reinfection
  - — Rarely used in the present era

Anti-inflammatory Therapy

■ Salicylates are indicated in the presence of acute, painful arthritis during the febrile phase.
- Duration of therapy is usually 4–8 weeks.
- Average initial amount prescribed should be ~50–75 mg/kg/d, in 4 divided doses.
- Extremely high doses are not required.

- Aspirin is used only to relieve symptoms and is usually associated with
  - Rapid and significant improvement in objective arthritis signs and symptoms
  - Almost immediate defervescence
- Specific blood levels do not need to be reached or maintained if clinical signs have disappeared.
- No evidence exists that salicylate administration affects clinical course or later cardiac involvement.
- High-dose aspirin may lead to significant side effects.
  - Tinnitus
  - Decreased hearing
  - Gastric irritation
  - Hepatotoxicity
- Several small studies comparing aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs) have demonstrated similar results in resolution of arthritis.
  - At this time, insufficient data exist to routinely recommend the use of NSAIDs in rheumatic fever.
- Administration of steroid hormones is indicated for severe cardiac involvement characterized by pancarditis with congestive heart failure.
  - Most commonly prednisone
- When myocarditis appears to be fulminant, steroid therapy has been shown to significantly improve survival.
  - No evidence of long-term palliative effects on chronic rheumatic valvular disease is available.
- Duration of steroid treatment may be extended to 1–3 months in severe cases.
  - Varying schedules of tapering dose.
  - Possible addition of salicylate therapy.
  - Studies comparing aspirin to steroids in prevention of long-term cardiac disease have not shown evidence of superiority.
- Specific therapeutic measures to control congestive heart failure may be useful.
  - Diuretics
  - Digitalis
- Furosemide (Lasix) is used for management of pulmonary congestion with left-ventricular failure.
- Digitalis (digoxin) should be administered cautiously.
  - The threshold for toxicity may be reduced in the presence of inflammatory myocarditis.
  - Withholding digitalis for 1 or 2 days until steroid therapy has begun to suppress the myocarditis may be prudent.
  - Serum potassium levels should be monitored because steroids and furosemide both decrease body potassium.
    - Predisposes patient to digitalis intoxication
- Enalapril is sometimes used in patients with mitral valve insufficiency.

Limitation of Activity

- The role of bed rest has been de-emphasized in recent years.
- For children with arthritis
  - Ambulation can be permitted when pain and joint tenderness improve.
- Patients with stable, mild cardiac involvement can be allowed to ambulate when they feel well enough.
- Patients with more severe carditis.
  - Length of restricted activity is individualized according to severity.

WHEN TO ADMIT

- All children with acute rheumatic fever should be hospitalized.
- Hospitalizing a child who has arthritis or carditis may be advisable for
  - Observation
  - Appropriate documentation of poststreptococcal illness
  - Initiation of treatment
- Hospitalization emphasizes to the parents
  - Seriousness of the disease
  - Importance of prophylaxis to prevent recurrence
- Specific association of Sydenham chorea with rheumatic fever.
  - Hospitalizing a child with this manifestation should not be mandatory if
    - Abnormal neuromuscular activity is mild.
    - Self-inflicted injury is unlikely.

WHEN TO REFER

- All children with acute rheumatic fever should be referred to a cardiologist for evaluation and management.

FOLLOW-UP

- Permitted physical activities
  - Children with mild mitral regurgitation with normal heart size should be allowed to engage in all athletic activities, except for the most strenuous, competitive sports.

- Children with more severe mitral regurgitation or aortic insufficiency with cardiomegaly should have
  - Some restriction of their activities
  - Continuing appropriate regimen
- If symptoms of fatigue or exercise intolerance persist despite medical management, full diagnostic evaluation should be performed.
  - Surgical intervention with valvuloplasty or valve replacement should be considered.

COMPLICATIONS

- In infancy, usually associated with
  - Severe carditis
  - Congestive heart failure
- In preschool-aged children
  - Polyarthritis caused by rheumatic fever is unusual.
  - Rheumatoid arthritis and other inflammatory diseases of the joint are more likely.
- In early childhood chorea is uncommon.
  - Most cases occur in patients >8 years.
- The major long-term consequence is the potential for inflammatory cardiac valvular involvement, leading to chronic heart disease.
- Ultimate development of rheumatic heart disease after a first attack can be correlated with severity of acute carditis.
  - A 10-year follow-up study of treatments begun in 1951 showed that patients developed chronic rheumatic heart disease (mitral insufficiency or stenosis or aortic regurgitation, or any combination).
    - ~30% of patients who had mild carditis
    - 50% of those who had moderate carditis
    - 75% with severe carditis
- Most children who develop rheumatic heart disease after a single attack of rheumatic fever have mitral regurgitation.
- Others either have mitral and aortic regurgitation or aortic regurgitation alone.
- Mitral stenosis evolves slowly.
  - Usually after repeated episodes of acute rheumatic fever
  - Sometimes unexpectedly
    - Many years after initial mild mitral valvulitis
    - Perhaps previously undiagnosed
  - Isolated mitral stenosis is
    - Unusual before early adulthood
    - Rare in developed nations
- Contraception and pregnancy.
  - Patients who have severe rheumatic heart disease are at high risk of cardiac complications during pregnancy and delivery.
    - Mitral stenosis has an especially high-risk profile.
    - Mild rheumatic heart disease is well tolerated during pregnancy.
  - Adolescent girls with rheumatic heart disease should be counseled about contraceptive methods.
  - Added cardiovascular burden during pregnancy.
    - Thorough obstetric care should be provided from the first trimester through delivery.
    - Prophylaxis against streptococcal infection should be continued.
    - Psychosocial support may be needed.
      - Especially for pregnant teenagers with significant rheumatic heart disease
    - If early termination is sought, therapeutic abortion should be performed in the hospital.

PROGNOSIS

- Murmurs.
  - In the months and years following an attack
    - Auscultatory findings frequently change from those heard during the acute episode.
    - Apical systolic murmurs heard initially may diminish or completely disappear.
    - Aortic diastolic murmur will almost always persist during the follow-up period.
  - An initial diagnosis of carditis does not necessarily imply progression to permanent heart damage.
  - In children labeled as having a history of acute rheumatic fever
    - Appellation of rheumatic heart disease must be reevaluated continually.
  - Even patients with severe carditis in the acute phase will show improvement in weeks and months after the recuperative period.
    - >50% of murmurs of mild or moderate mitral insufficiency will disappear completely.
- Other manifestations are self-limiting with no late sequelae.
- Arthritis clears without joint dysfunction or deformity.
- Chorea leaves no neuromuscular impediment.
- Recurrence of rheumatic fever.
  - Striking tendency to recur.
  - Before the introduction of preventive measures, most patients who had initial attack of rheumatic fever had ≥1 recurrences.
  - Recurrence rate is highest during first 3 years after initial attack.
  - Diminishes with time after original episode.
  - Rare in adulthood.

PREVENTION

Rheumatic Fever

- The major goal is preventing an initial attack, which can be accomplished by effective treatment of acute GAS pharyngitis.
- Primary prevention programs have demonstrated efficacy of identifying streptococcal infection by
  - Throat cultures for susceptible children
  - Early treatment
- Secondary prevention in the form of antistreptococcal prophylaxis after the first attack has significantly reduced
  - Recurrence
  - Effects of repeated bouts of carditis

Recurrence

- Preventing recurrent attacks that carry risk of heart involvement and further cardiac damage is most important.
- Antibiotic prophylaxis in a patient with known rheumatic fever is protection against recurrence through prevention of GAS infection.
  - Continuous antimicrobial prophylaxis should be implemented in all children who have a history of rheumatic fever, including those who present with chorea.
- Prophylaxis as follows:
  - Children with initial cardiac involvement but no evidence of residual heart disease: for 10 years or until age 21 years (whichever is longer)
  - Patients with persisting chronic mitral or aortic valvular disease: until age 40 years
  - Children with no cardiac involvement during initial attack: for 5 years
- The most effective method for reducing streptococcal infections and rheumatic fever recurrence.
  - Intramuscular injections of long-acting penicillin (benzathine penicillin G, 600,000 units for children weighing ≤60 lb or 1,200,000 units for those weighing >60 lb)
- Preventive regimen most effective when given every 3–4 weeks.
  - In residual cardiac involvement
    - Every-3-week regimen for the first 6–12 months
    - Continue every 3–4 weeks for at least a 1- or 2-year period
    - Followed by oral prophylaxis
- Parenteral therapy is the most effective method of prophylaxis.
  - Strict adherence to daily oral medication is especially difficult for children and adolescents.
  - Transient discomfort at the injection site (anterior thigh or buttock) may be relieved by a hot bath on the evening of injection.
- Alternative methods of prophylaxis include
  - Oral administration of penicillin V
    - 250 mg twice a day
  - Sulfadiazine or sulfisoxazole
    - 0.5 g once daily for patients weighing ≤60 lb and 1.0 g once daily for those weighing >60 lb
- For the patient sensitive to both penicillin and sulfisoxazole
  - Consider daily prophylaxis with another agent.
  - Successful oral prophylaxis is hard to maintain.
    - If used, constantly reinforce its value and need for compliance.
  - Rheumatic fever recurrence is less likely after 2–5 years.
- Patients with chronic rheumatic heart disease.
  - Oral regimen can be substituted for intramuscular penicillin.
  - Oral prophylaxis can be instituted immediately for patients who did not have carditis during the acute attack.
  - Under these circumstances, recurrences with carditis are extremely rare.

Bacterial Endocarditis

- Individuals with a history of rheumatic fever without evidence of significant murmurs on follow-up examination
  - Are not susceptible to bacterial endocarditis.
  - Do not have damaged heart valves.
- Recent guidelines from the AHA report that patients with heart disease
  - Are more likely to get infective endocarditis from frequent exposure to random bacteremic events associated with daily activities
  - Are less likely to get infective endocarditis from bacteremia following dental or surgical procedures
- Latest guidelines for prevention of infective endocarditis recommend antibiotic prophylaxis for patients with
  - Prosthetic cardiac valves
  - Previous infective endocarditis
  - Certain types of repaired and unrepaired congenital heart diseases
- Antibiotic prophylaxis before dental or surgical procedures is no longer recommended for patients with mitral or aortic valve disease following rheumatic fever.
- Recommendations for prevention of recurrent episodes of rheumatic fever have not changed.

DEFINITION

- Rocky Mountain spotted fever (RMSF) is an acute infectious disease.

SIGNS AND SYMPTOMS

- Characterized by
  - Fever
  - Headache
  - Myalgia
  - Distinctive exanthem
- After inoculation with rickettsiae
  - Incubation period ranges from 2–12 days.
  - The usual period is 5–7 days.
  - Shorter incubation periods are associated with more serious disease.
- The prodromal period lasts 2–3 days, predominated by
  - Low-grade fever
  - Chills
  - Muscle aches
- Muscle pain is most common in the calf region in younger patients.
- Headache is an early symptom.
  - Infants and toddlers may express pain from headache or myalgias as crying or fussiness.
- Other frequent symptoms include
  - Malaise
  - Anorexia
  - Vomiting
  - Photophobia
- The prodrome is followed by accentuation of symptoms.
  - Especially fever.
    - Temperatures are often as high as ≥40°C (104°F).
    - The lowest temperatures, although still elevated, are recorded in the mornings.
  - Lethargy and mental obtundation become prominent.
  - Symptoms seen at this stage are not diagnostic.
- Rash is the most distinctive sign.
  - Usually appears 3–5 days after onset of fever.
  - Begins peripherally on
    - Wrists
    - Ankles
    - Hands
    - Feet
  - Initially, the lesions are
    - Macular
    - Discrete
    - Erythematous
    - Blanch on pressure
  - Rash rapidly spreads centrally, involving
    - Arms
    - Legs
    - Axillae
    - Buttocks
    - Trunk
    - Neck
    - Face
  - Lesions deepen in color, becoming
    - Dusky red
    - Maculopapular
    - Petechial
      - True petechiae may not form until day 6 of illness.
      - 35%–60% of patients never develop petechiae.
      - Petechial lesions may coalesce and form large ecchymotic areas.
      - In severe cases and when treatment is delayed, these ecchymotic areas may ulcerate.
      - Distal regions (eg, fingers and toes) may become gangrenous in as many as 4% of cases.
  - As many as 15% of patients do not develop rash, or they develop a fine rash that may be difficult to appreciate in patients with darker skin tones.
  - Rash does not occur until day 4 of the illness.
  - Petechiae may be a much later finding.
  - Some patients never develop a discernible exanthem.
- Tachycardia and an elevated pulse rate are noted early and are proportional to the degree of hyperpyrexia.
- A sudden increase in pulse rate or a decrease in blood pressure may indicate
  - Peripheral circulatory collapse
  - Severe bleeding
  - Myocardial failure
- Photophobia is associated with conjunctival ecchymosis involving bulbar and palpebral conjunctivae.
- Other manifestations include
  - Abdominal pain.
  - Retinal hemorrhages.
  - Vomiting.
  - Hepatomegaly.
  - Splenomegaly with generalized abdominal tenderness.
  - Lethargy.
  - Obtunded state of consciousness.

- Jaundice is not usually seen except in the most critically ill patients, with disseminated intravascular coagulation (DIC).

- Diminished urinary output caused by
  - Fever.
  - Poor fluid intake from nausea.
  - Vomiting.
  - Mild azotemia caused by fluid losses should respond to rehydration.
- The patient may exhibit nuchal rigidity, resulting from vasculitic reaction in the meninges.
- Neurologic manifestations include
  - Disorientation
  - Confusion
  - Seizures
  - Coma
  - Central deafness
  - Cortical blindness
  - Sixth nerve palsies
- Causes of neurologic effects include
  - Vasculitis
  - Hemorrhage from coagulopathies
  - Secondary metabolic changes caused by circulatory collapse

DIFFERENTIAL DIAGNOSIS

- Neurologic and abdominal symptoms early in RMSF may mask its diagnosis.
- Illnesses to be considered and differentiated from RMSF, especially after the rash appears, include
  - Rubeola (measles)
  - Meningococcemia
  - Henoch-Schönlein purpura
  - Kawasaki disease
  - Immune thrombocytopenic purpura
  - Leukemia
  - Typhus
  - Ehrlichiosis
  - Infectious mononucleosis
- Meningococcemia.
  - Petechial rash of meningococcemia differs from that of RMSF in
    - Distribution
    - Rapid extension
    - Coalescence of lesions into larger hemorrhagic, purpuric areas
  - Prostration develops rapidly if the patient remains untreated.
    - Often apparent on admission to the hospital
  - Helpful points in differentiating meningococcemia from RMSF include
    - Absence of myalgia
    - Extremely abrupt onset
  - Leukocyte count may be elevated in meningococcemia.
  - The sickest patients are frequently leukopenic.
  - Other presentations include
    - Meningitis with pleocytosis
    - Low glucose levels
    - Organisms in the cerebrospinal fluid (CSF)
  - Distinguishing between these entities clinically is not often possible.
    - Treatment for both diseases in an ill patient is warranted.
- Ehrlichiosis.
  - Rickettsial disease with clinical similarity to RMSF.
  - Rash occurs with less frequency.
    - >60% of children with ehrlichiosis have been noted to have rash.
    - Variable in location and appearance.
    - May be petechial.
    - Can be confused with rickettsial exanthems.
  - Early diagnosis and treatment with doxycycline reduces morbidity.
- Rubeola (measles).
  - Characterized by a macular rash.
    - Infrequently becoming hemorrhagic
  - Begins on the face and neck.
  - Preceded by
    - An exanthem
    - Koplik spots on the buccal mucosa
  - Coryza and cough in the prodromal stage of illness are not consistent with RMSF.
  - A history of adequate immunization with rubeola vaccine greatly diminishes this possibility.
- Henoch-Schönlein purpura.
  - May produce a petechial or purpuric rash, frequently concentrated on lower extremities and buttocks.
  - Cutaneous lesions may be multiform.
  - May occur on other parts of the body.
  - Arthralgia with periarticular swelling and accompanying signs and symptoms of upper respiratory tract inflammation, intense abdominal pain, or nephritis.
- Kawasaki disease.
  - Fever.
  - Puffy hands and feet.

- Rash.
  - Typically does not begin peripherally and spread centrally or become petechial in 1–2 days
- Conjunctival injection.
- Usually, Kawasaki disease is not seriously considered until the following occur:
  - 5 days of fever
  - Enlarged cervical node
  - Pharyngeal hyperemia
  - Dry cracked lips
  - Strawberry tongue
  - Marked irritability
- Leukocyte and erythrocyte sedimentation rates are usually elevated significantly.
- Kawasaki disease usually occurs in the winter and spring months.
- Children with Kawasaki disease do not give a history of tick exposures.
- Elevated platelet count begins during the second week of illness.

■ Other illnesses that produce petechiae and lack distinctive distribution of rash include
- Immune thrombocytopenic purpura.
  - Seen as a petechial rash in an otherwise healthy patient
- Patients with leukemia who initially have fever and petechiae would be expected to
  - Be anemic.
  - Have lymphadenopathy.
  - Have hepatosplenomegaly.
- Patients with infectious mononucleosis with petechial eruption usually have
  - Lymphadenopathy
  - Hepatosplenomegaly
  - Gradual onset
- Typhus is a rickettsial infection to be excluded.
  - Murine typhus produces a milder disease.
    - Rash is macular, not petechial.
  - Epidemic typhus may produce a petechial rash that typically begins proximally and extends peripherally.
  - Does not usually involve the palms or soles.
  - History of a tick bite is absent.

DIAGNOSTIC APPROACH

■ The diagnosis is made clinically.
■ Clinical diagnosis and treatment are typically required before laboratory confirmation.
■ The disease still has a significant risk of morbidity and mortality when treatment is delayed.

LABORATORY FINDINGS

■ Available laboratory tests to confirm the presence of *Rickettsia rickettsii* include
- Increase in antibody titer detected by immunofluorescence or latex agglutination
- Polymerase chain reaction (PCR) testing
- Immunofluorescence of skin biopsy
- Isolation of organism from clinical specimen

■ Immunofluorescent staining of the skin biopsy specimen.
- May identify *R rickettsii.*
- May provide early proof of RMSF.
- Not readily available to most clinicians.
- Appropriate antibiotic therapy started 3 days before biopsy has resulted in negative immunofluorescence.
  - When appropriate treatment has been initiated before biopsy, clinical criteria justify a full course of antibiotic therapy.

■ PCR testing provides a specific diagnostic tool for early diagnosis.
- Expensive
- Not commonly available

■ Complement fixation and immunofluorescent antibody studies in serum will identify patients with RMSF.
- Test results do not become positive until 7–10 days after the onset of illness, or later if antibiotic therapy has begun early.
- Titers should be performed during the acute illness.
- Repeat 3 weeks later.
- 4-fold increase in titer in the convalescent sera is diagnostic for infection.

■ Weil-Felix test is at best a nonspecific test for RMSF.
- Agglutination of *Proteus vulgaris* by the patient's serum.
- Acute and convalescent sera must be compared.
- Proteus agglutinins may appear by the end of the first week of illness.
- Availability of more specific and sensitive tests makes this test obsolete.

■ Rickettsiae can be isolated from body fluid or tissue specimens when grown in laboratory animals or chick embryos.
- The high rate of disease transmission to laboratory technicians makes such techniques feasible only in laboratories engaged in *Rickettsia*-related research in which all workers are immunized.

- Culture identification of rickettsiae is not available in most clinical settings.

- Blood leukocyte counts and differential counts are usually within reference ranges, but neutrophils often predominate.
  - Neutrophil predominance may help distinguish RMSF from ehrlichiosis.
  - Most patients with ehrlichiosis have lymphopenic leukopenia.
  - Thrombocytopenia is a complication seen in the later stages of the disease.
    - May be the result of platelet adherence to damaged endothelium
- ≤20% of patients may have hyponatremia.
  - Possibly caused by increased vascular permeability of the kidney to sodium.
  - Nonspecific finding; does not exclude other diagnoses, such as ehrlichiosis.
  - The remainder of electrolyte profile is usually normal.
  - Hypochloremia is seen in some.
  - ≤25% of patients will display increased blood urea nitrogen levels and increased liver enzymes.
  - With the development of DIC, abnormalities can occur.
    - Prothrombin time
    - Partial thromboplastin time
    - Fibrinogen
    - Fibrin split products
- Patients with neurologic manifestations may have reference CSF cell counts.
  - Most have reference CSF glucose and protein levels.
  - CSF analysis might reveal
    - Neutrophilic or lymphocytic pleocytosis
    - Elevated protein
  - Nonspecific findings; may not help distinguish RMSF from meningococcal disease or ehrlichiosis.
- Long-term morbidity from neurologic complications, though rare, is still significant.
  - Hematuria and anemia may occur.
  - Transfusion or renal dialysis is rarely required.

DIAGNOSTIC PROCEDURES

- Skin biopsy

TREATMENT APPROACH

- Treatment should never be withheld or delayed due to
  - Absence of rash
  - Lack of exposure to ticks
  - Desire to await confirmatory laboratory study results
  - Patient location where RMSF is uncommon
  - Pediatrician discomfort using doxycycline in a child <8 years
- Treatment for RMSF mandated until the diagnosis can be excluded if
  - Triad of fever, headache, and myalgia
  - Combined with a history of tick bite or removal within the previous 2 weeks
- If a pediatrician strongly suspects RMSF because of patient's clinical history and physical findings, therapy should be initiated immediately.
  - Can be administered concurrently with treatment for meningococcemia

SPECIFIC TREATMENTS

Pharmacotherapy

- Doxycycline
  - Drug of choice for all ages.
  - Given and continued for ≥3 days after clinical improvement and defervescence.
  - Usual length of therapy is 7–10 days.
  - Intravenous (IV) therapy should be given to all ill patients.
  - Transition to oral therapy when the patient's condition has improved.
  - Effective against ehrlichiosis, which may mimic RMSF.
  - Has a broad therapeutic index.
  - Levels do not need to be monitored as required with other RMSF medications, such as chloramphenicol.
- Tetracycline
  - Shown to be effective against RMSF.
  - Can lead to increased dental staining compared with doxycycline in children <9 years.
  - No more effective than doxycycline.
  - Tetracycline is less commonly used in children.
- Chloramphenicol
  - No longer the drug of choice for RMSF.
  - Data have shown it may be more effective than doxycycline.
  - The toxic effects of this drug (aplastic anemia) make it an undesirable treatment option.
  - May be given to patients who cannot tolerate doxycycline or tetracycline.
- Combination therapy
  - Initiating treatment for meningococcal disease, as well as RMSF and ehrlichiosis, in an ill patient may be necessary.

- When this situation arises, doxycycline will treat ehrlichiosis and RMSF.
- Can be used in conjunction with an extended spectrum cephalosporin to treat meningococcal infection.

Hospitalization

- Desirable initially for most patients to
  - Confirm diagnosis.
  - Observe effect of therapy.
- Therapy should be continued until the patient has improved and has been afebrile for 72 hours.
  - Generally occurs after 7–10 days of therapy
- Supportive therapy.
  - Includes maintenance of hydration and nutrition with appropriate IV fluids and oral feedings (if tolerated).
  - Management of DIC may include therapeutic maneuvers, such as administering
    - Fresh-frozen plasma
    - Fresh platelets
    - Packed red blood cells
    - Vitamin K
  - Seizures may require the use of anticonvulsant medications.

WHEN TO ADMIT

- Most patients need to be admitted and kept hospitalized until they show clinical improvement.
- Hemodynamic instability.
- Dehydration.
- Requires intensive monitoring.
- RMSF with its complications.

WHEN TO REFER

- Uncertain diagnosis
- Clinical suspicion of disease

COMPLICATIONS

- Vascular necrosis and thrombosis may result in local gangrene and loss of tissue.
- DIC may develop (uncommon).
  - Patients with this complication have the greatest risk of dying.
- Myocardial failure may result from myocarditis and arrhythmias.
- Edema may be generalized as a result of
  - Increase in capillary permeability caused by the vasculitis
  - Heart failure
  - Iatrogenic fluid overload
  - Any combination
- Long-term morbidity from neurologic complications is rare but still significant.
- Hematuria and anemia may occur.
  - Transfusions or renal dialysis are rarely required.

PROGNOSIS

- Mortality of ~0.5%–4.0% in recognized cases.
  - Patients who escaped clinical detection have been identified by serologic evidence.
    - Disease may occur in a mild or subclinical form.
- Rocky Mountain *spotless* fever has also been described.
  - Suggestion that patients who have spotless *or* almost spotless fever have a significantly higher mortality as a result of delayed diagnosis and treatment
- RMSF can be considered a potentially fatal illness.
  - Younger patients are likely to be less severely affected than older patients.
- Early diagnosis and prompt therapy lessen disease severity.
  - Under such circumstances, death would be extremely unusual.
  - In most patients, early clinical diagnosis and adequate therapy shorten the duration of illness appreciably.
- Recovery from the illness is accompanied by immunity to *R rickettsii*.

PREVENTION

- Repellents have been shown to be effective against ticks.
  - *N,N*-Diethyltoluamide (DEET) skin repellents
  - Permethrin-containing repellents used on clothes
- Systemic reactions to DEET are possible when the repellents contain a high concentration of the chemical.
- The best preventive measure is avoidance of tick exposure.
- When exposure is likely, daily searches for ticks should be performed.
  - In tick-infested areas, twice-daily searches are advised.
  - Careful inspection at bath time is an excellent way to discover ticks.
- Ticks may be removed by gentle traction with forceps or tweezers.
  - Care must be taken not to crush them.
  - Skin should be disinfected before and after tick exposure to remove feces that may carry *R rickettsii*.

- The tick should never be covered in
  - Petroleum jelly
  - Nail polish remover
  - Alcohol
- No one should attempt to burn the tick to coax it to detach itself.
  - These attempts may lead the tick to defecate or aerosolize infected body fluids.

■ Antimicrobial prophylaxis is not indicated after a tick bite.
- The chance of a tick carrying the disease, even in an endemic area, is low.
- No demonstrable benefit of prophylaxis has been found.

BACKGROUND

- Anemia may be defined by
  - Laboratory values (low hemoglobin level)
  - Physiologic consequences (inadequate oxygen-carrying capacity)
- Associated and commonly encountered pediatric conditions
  - Sickle cell disease
  - Iron deficiency

GOALS

- Screening programs are directed primarily at detecting disease in otherwise asymptomatic children.
  - Iron deficiency is a significant public health issue.
    - Prevalence in US toddlers aged 1–2 years: 7%, increasing to 9%–16% among adolescents (National Health and Nutrition Examination Survey 1999–2000).
    - Adequate iron stores are critical for normal neurocognitive development.
- Sickle cell disease affects ~100,000 Americans.
  - Early identification helps prevent deaths and complications.
  - Newborn screening and rapid institution of penicillin prophylaxis has helped prevent death and other complications, including a dramatic decrease in the incidence of fatal pneumococcal sepsis.
  - Without screening, sickle cell disease may go undetected until the child presents with a life-threatening complication.

GENERAL APPROACH

- Screening for anemia begins with newborn hemoglobinopathy screening programs.
  - Many of the variant hemoglobins are benign, particularly when patients are heterozygous.
  - Newborn screening improves sensitivity of detection for α-thalassemia.
  - β-thalassemia may not be detectable until after hemoglobin switching from fetal forms has been completed at 6–12 months of age.
  - Sickle cell disease.
    - Measures are available to prevent life-threatening complications in children identified early. These include
      - Penicillin prophylaxis (125 mg orally twice daily)
      - Education (including parental ability to correctly palpate splenic size)
      - Referral to a pediatric hematology program
      - Timely immunization
      - Genetic counseling before a subsequent pregnancy
  - The American Academy of Pediatrics recommends next screening at 9–12 months.
- Children at risk for iron deficiency anemia include
  - Preterm and low birth weight neonates
  - Infants fed with cow's milk <12 months
  - Breastfed infants not receiving iron supplementation >6 months
  - Formula-fed infants who do not receive iron-fortified formulas
  - Children aged 1–5 years who ingest >24 oz of cow's milk per day
  - Children with special health care needs
  - Children with low socioeconomic status
- Starting in adolescence, all nonpregnant women should be screened for anemia every 5–10 years throughout their childbearing years.
  - Those with risk factors for iron deficiency (eg, extensive menstrual or other blood loss, low iron intake, previous diagnosis of iron deficiency anemia) should be screened annually.
- Adolescent males need to be screened for anemia only in the presence of risk factors.

SPECIFIC INTERVENTIONS

- Whole-blood hemoglobin concentration is measured using blood obtained by skin puncture of the finger or heel.
  - The sample may be analyzed using a small portable spectrophotometer or a benchtop particle counter.
  - Hemoglobin concentration is compared with reference values for age-matched typical children.
    - Anemia is defined as a level less than the lower reference limit (2 standard deviations below the mean).
- Positive screening test results must be confirmed and correlated with clinical presentation.
  - Venous blood sample anticoagulated with ethylenediaminetetraacetic acid submitted for
    - Complete blood cell count
    - Microscopic examination of a Wright-stained peripheral blood smear
- Other helpful iron status studies include
  - Serum ferritin (most reliable indicator of iron status/stores in the absence of an underlying inflammatory illness)
    - Serum ferritin <15 ng/mL confirms diagnosis of iron deficiency.

- Serum iron
- Iron-binding capacity
  - Best obtained in the fasting state; findings may be misleading if the patient has recently eaten an iron-rich meal
- Lead level
  - Younger children may be more prone to lead intoxication secondary to pica associated with iron deficiency.

Differential Diagnoses

- Iron deficiency anemia will generally have hypochromic microcytic indices.
  - Low mean corpuscular volume
  - Low mean corpuscular hemoglobin concentration
  - High red cell distribution width
  - May be associated with thrombocytosis
    - Thrombocytopenia may be observed in severe iron deficiency.
- Types of anemia that should be included in the differential diagnosis of microcytic anemia include
  - Thalassemia
  - Sickle cell–thalassemia disease
  - Some hemoglobinopathies (C and E)
  - Severe lead intoxication
  - Anemia of chronic disease
  - Hereditary spherocytosis
- For additional information on differential diagnoses, see Anemia and Pallor.

Management

- Mild microcytic anemia (ie, hemoglobin level 8–10 g/dL).
  - Empiric treatment with iron supplementation (3–4 mg elemental iron/kg daily) is appropriate.
  - Reticulocyte count should increase within 1 week of beginning iron therapy.
  - The hemoglobin level should increase by at least 1 g/dL within a month.
    - Treatment should continue for an additional 2 months in patients who respond.
  - Appropriate dietary counseling is important to prevent recurrence.
  - For patients who fail to respond
    - Additional laboratory evaluation is indicated.
    - Referral to a hematologist should be considered.
    - An evaluation should be undertaken to identify sources of occult blood loss.
      - Particularly in older children who are not consuming significant amounts of cow's milk.
      - Inadequate response may be related to continued blood loss (eg, heavy menses, occult gastrointestinal bleeding), inflammation, ineffective absorption, or poor adherence to treatment.
- In moderate to severe anemia (hemoglobin [Hb] <8 g/dL), immediate referral to a pediatric hematologist may be appropriate.
  - Especially for children who are symptomatically anemic (eg, elevated heart or respiratory rate, failure to thrive, fatigue).
  - Hospitalization may be required for further evaluation and management (especially for severe anemia, Hb <5–6 g/dL).
- If anemia is severe, confirmatory laboratory evaluation should be done when empiric iron therapy is begun (4–6 mg elemental iron/kg of body weight/d).
- Interpretation of newborn hemoglobinopathy screening results.
  - FA: normal (predominantly HbF [$\alpha_2\gamma_2$], some HbA [$\alpha_2\beta_2$]).
  - FAS: sickle cell trait (predominantly HbF, some HbA, with less HbS [$\alpha_2\beta^S{}_2$]).
  - FS: sickle cell disease (predominantly HbF, some HbS).
  - FSC: sickle cell disease (predominantly HbF, some HbS, with less HbC [$\alpha_2\beta^C{}_2$]).
  - FSA: sickle cell disease with β^+-thalassemia (predominantly HbF, some HbS, with less HbA).
  - + Bart: α-thalassemia (Bart Hb [γ_4]).
  - Children with an FS pattern will likely have 1 of 2 forms of severe sickle cell disease, HbSS (homozygous β S) or HbSβ 0-thalassemia (compound heterozygote for β S and a β-thalassemia major mutation).
  - Children with an FSC pattern also will have a severe form of sickle cell disease, HbSC, caused by compound heterozygosity for both β S and β C.
  - In contrast, children with an FSA pattern, who still express some normal adult HbA (usually owing to compound heterozygosity for β S and a β-thalassemia minor mutation), can be expected to have a milder course of disease.
- Management following abnormal newborn hemoglobinopathy screening results.
  - The parents of children with an FAS pattern (sickle cell trait) should be referred to a genetic counselor for additional education on their risk for having a child with sickle cell disease or carrier status.

- Children with an FS, FSC, or FSA pattern have some form of sickle cell disease and should be prescribed penicillin prophylaxis (125 mg orally twice daily) as early as possible—optimally by 8 weeks of age—and be referred to a pediatric sickle cell program.

Screening for Genetic-Metabolic Diseases 988

BACKGROUND

- Newborn screening is a public health program run by states.
- Association of Public Health Laboratories maintains current information on
  - Conditions for which states conduct screening.
  - Contact information for newborn screening coordinators in each state.
  - Information can be accessed at www.newsteps.org.
- Health care professionals must familiarize themselves with their state's newborn screening panel.
- Even though the newborn screening program is for conditions, the screening itself is for analytes.

GOALS

- To screen for disorders for which early detection and treatment will improve outcome
- In 2006, a Uniform Screening Panel of 29 conditions was recommended as a minimal list for all states and programs, including
  - Hypothyroidism
  - Hemoglobinopathies
  - Congenital adrenal hyperplasia
  - Cystic fibrosis
  - Galactosemia
  - Biotinidase deficiency
  - 22 disorders of amino acid, fatty acid, and organic acid metabolism
  - Hearing loss (not a blood test)
- Recent additions include
  - Severe combined immune deficiency
  - Cyanotic congenital heart disease (not a blood test)
  - Pompe disease (glycogen storage disease type 2) (approved in 2015)

GENERAL APPROACH

- Heel prick to collect blood on a blood spot card.
  - Sample should be collected after 24 hours of age and no later than 48 hours of age.
  - Timing of collection can be modified for neonates who
    - Received a transfusion or total parenteral nutrition
    - Were born outside a hospital (eg, home birth)
- Results are stratified based on the level and ratio of analytes.
  - In general, the results fall into 3 categories.
    - Negative screening result: no follow-up required
    - Positive screening result: repeat newborn screening recommended
    - Positive screening result: urgent evaluation, diagnostic testing, and treatment initiation recommended
- All newborns who screen positive should be examined by the primary care pediatrician and the result explained to parents.
- Newborn screening for metabolic conditions uses measurement of enzyme activity or analytes.
  - Primary metabolites whose abnormal levels may be caused by a specific metabolic disorder
  - Secondary metabolites whose levels and ratios make the testing more precise
  - Disorders, not part of the main list, whose presence might be recognized by abnormalities of amino acids or acylcarnitines
- Newborn screening is not diagnostic for any condition.
  - The American College of Medical Genetics and Genomics published open-access newborn screening action sheets to guide primary care pediatricians on initial management and follow-up testing.
  - Expertise from a local or regional genetic-metabolic team should always be available.
  - Genetic counseling can help families understand the disorder, its causes, and the implications for other family members.
  - False-negative results do occur.
- When a patient presents with features suggesting one of the inborn errors for which newborn screening has already been done, it is prudent to do the appropriate diagnostic test for that disorder.
- Most inborn errors of metabolism will require lifelong dietary limitation of the toxic amino acid intake.
  - Restriction of natural proteins
  - Supplementation with special formula devoid of the toxic amino acids
  - Provision of adequate calories
- Infants with most inborn errors of metabolism, except for those with severe galactosemia, will tolerate some breastfeeding.
- Patients on special diets typically need regular assessment of intake and nutritional status and serial laboratory testing.
- General sick day management.
  - Metabolic decompensations are typically triggered by infection, fasting, and dietary indiscretions.
  - Recognize impending acute crisis early; symptoms include
    - Poor feeding
    - Vomiting
    - Fever

SPECIFIC INTERVENTIONS

Low or Absent Biotinidase

- Clinical characteristics
  - Most neonates are asymptomatic at birth and usually do not become symptomatic until 4–5 months of age.
  - Symptoms, when present, typically involve skin, brain, and immune systems.
    - Alopecia, eczema, and dermatitis
    - Hypotonia, seizures, developmental delays, sensorineural hearing loss, and progressive optic atrophy
    - Frequent infections
  - Associated metabolic acidosis can cause vomiting and hyperpnea.
  - With newborn screening and early treatment initiation, biotinidase-deficient patients should remain asymptomatic for life.
- Newborn screening and diagnostic testing
  - Semiquantitative colorimetric assay to measure biotinidase enzyme activity.
    - If low or absent
      - Quantitative serum biotinidase enzyme assay
      - Plasma acylcarnitine profile
      - Urine organic acid analysis
  - Genetic analysis of biotinidase gene is usually conducted to understand the basis of deficiency and estimate severity.
  - Serum biotin measurement is not a sensitive indicator of biotin deficiency.
- Management
  - Neonates with positive screening results should be started empirically on 10 mg of oral free biotin daily.
  - Relying solely on dietary sources of biotin is not recommended.
  - Families should be advised to avoid raw egg white; cooked eggs are safe.
  - If deficiency is not diagnosed until symptoms develop, sensorineural hearing loss, optic atrophy, and developmental delays may not be reversible.

Low Galactose-1-phosphate Uridylyltransferase

- Clinical characteristics
  - Onset and severity depend on the degree of galactose-1-phosphate uridylyltransferase (GALT; sometimes called Gal-1-PUT or UDPGT) enzyme deficiency.
  - Classic galactosemia (GALT activity of 0%–5% of normal) typically manifests 1–2 weeks after milk is introduced.
  - Symptoms include
    - Poor feeding
    - Poor weight gain
    - Vomiting
    - Diarrhea
    - Lethargy
  - Septicemia (especially *Escherichia coli* sepsis) is common and can be the presenting feature.
  - Cataracts can develop within a few weeks, or later.
  - Physical examination may reveal jaundice, hepatomegaly, signs of coagulation abnormalities, hypotonia, and bulging fontanels.
  - Abnormality may be present in
    - Liver (mixed conjugated and unconjugated hyperbilirubinemia, elevated aspartate aminotransferase and alanine aminotransferase levels, coagulation abnormalities)
    - Kidneys (renal tubular acidosis, galactosuria, glucosuria, aminoaciduria, proteinuria)
  - Late manifestations include developmental delays, especially in speech and language development; ataxia; and premature ovarian insufficiency.
    - No correlation seen with the degree of dietary control
  - Duarte variant galactosemia.
    - GALT activity ~25% of normal
    - Enzyme activity sufficient to prevent acute catastrophic consequences of severe GALT deficiency
  - Classic galactosemia can become symptomatic before screening results are reported.
    - Thus, galactose should be excluded from the diet immediately if clinically suspected.
- Management
  - Mainstay of management is a galactose-free diet where human and cow milk are replaced with soy milk.
  - If liver disease is significant at diagnosis, an elemental formula with medium-chain triglycerides may be used transiently.
  - Liver biopsy is rarely needed.
  - Dietary treatment typically leads to rapid and complete recovery.
    - Liver and renal dysfunction usually resolve in 1–2 weeks.
    - Cataracts, if present, may resolve slowly.

- Dietary treatment does not alter the course of the late manifestations.
  - Girls need to be monitored closely for signs of primary or secondary amenorrhea; those with ovarian insufficiency can benefit from hormone replacement therapy.
- There is no universal agreement on dietary management for Duarte variant galactosemia.
  - Duarte variant galactosemia does not cause premature ovarian insufficiency.

Results Suggesting Amino Acid Disorders

- Summary of analytes and the follow-up diagnostic testing for amino acid disorders covered by newborn screening is in **Table 1.**

Elevated Phenylalanine With Low Tyrosine on Newborn Screen

- Phenylketonuria (PKU)
  - Clinical characteristics
    - Classic PKU in neonates with complete deficiency.
    - Hyperphenylalaninemia in neonates with partial deficiency.
    - Untreated classic PKU results in global developmental delays, intellectual disability, and seizures.
    - With treatment, classic PKU can be clinically silent or manifest only subtle neuropsychiatric features.
      - Slowing of executive functioning, attention-deficit/hyperactivity disorder, depression, anxiety
  - Newborn screening and diagnostic testing
    - Elevated phenylalanine and phenylalanine to tyrosine ratio on the newborn screen using tandem mass spectrometry (MS/MS) is reported as a positive result.
    - Elevations are categorized as mild to moderate or severe.
      - Mild to moderate elevations require repeat newborn screening before diagnostic testing is considered.
  - Management
    - Normal blood phenylalanine level is 1–2 mg/dL (60–120 μmol/L); no treatment is needed if the blood level is <6 mg/dL (360 μmol/L).
    - Restriction of dietary phenylalanine is the mainstay of treatment if phenylalanine levels are >360 μmol/L.
    - The goal is to achieve a plasma phenylalanine level of 2–6 mg/dL (120–360 μmol/L).
    - Restricting phenylalanine intake to the amount tolerated severely restricts total protein intake, so special metabolic formulas and foods that provide extra tyrosine without phenylalanine must be used.
    - Neonates with severe phenylalanine hydroxylase (PAH) deficiency may tolerate only 250–300 mg per day of phenylalanine.
    - Sapropterin dihydrochloride (synthetic tetrahydrobiopterin) is an adjunct to diet modifications that allows patients to eat more regular popular protein foods.
    - Sick day management.
      - Anticipate increase in plasma phenylalanine level.
      - Brief periods of elevated phenylalanine do not have long-term consequences.
      - No urgent dietary changes are necessary.
- Maternal PKU (MPKU)
  - Poorly controlled MPKU is teratogenic and will result in a spectrum of developmental anomalies called the MPKU syndrome.
    - Features include microcephaly, intrauterine growth restriction, congenital heart defects, and severe intellectual disability.
  - Mother's phenylalanine level should be <6 mg/dL before conception and during the pregnancy.
  - Frequent monitoring is required.
  - Fetal echocardiography should be considered at 20–22 weeks of gestation.
  - Breastfeeding is safe, unless the neonate also has PAH deficiency.

Elevated Leucine Plus Isoleucine on Newborn Screen

- Maple syrup urine disease (MSUD)
  - Clinical characteristics
    - Age at onset and severity depend on the degree of branched-chain keto acid dehydrogenase enzyme complex deficiency.
    - Clinical groups include neonatal "classic," intermediate, intermittent, thiamine responsive, and E3 deficient.
    - Encephalopathy is the main manifestation, with elevated leucine thought to be the primary neurotoxin.
    - Classic MSUD presents with encephalopathy that can progress to cerebral edema and herniation.
    - Most severe MSUD will result in some degree of permanent intellectual disability.

Table 1. Amino Acid Disorders

Elevated Analyte on Newborn Screen	Possible Disorders	Diagnostic Testing
Phenylalanine, phenylalanine to tyrosine ratio	**PKU**, hyperphenylalaninemia, BH4 deficiency, DHPR deficiency	Plasma amino acid profile, PAH genotyping, urine pterin testing
Leucine, isoleucine (and hydroxyproline, which shares the same atomic mass)	**MSUD**, hydroxyprolinemia	Plasma amino acid profile, urine organic acid analysis
Methionine	**Homocystinuria (CBS deficiency)**, MAT I/III deficiency, GNMT deficiency, AdoHcy hydrolase deficiency, tyrosinemia, liver disease/injury	Plasma amino acid profile, plasma total homocysteine, plasma vitamin B_{12} level, urine organic acid analysis
Tyrosine, succinylacetone	Tyrosinemia (TAT deficiency, 4-HPPD deficiency), liver disease/injury	Plasma amino acid profile, urine organic acid analysis
Succinylacetone	**Tyrosinemia type I (FAH deficiency)**	
Citrulline	**Citrullinemia type I**, citrullinemia type II (citrin deficiency), **argininosuccinic acidemia**	Plasma ammonia level, plasma amino acid profile, urine organic acid analysis

Abbreviations: AdoHcy, S-adenosylhomocysteine; BH4, tetrahydrobiopterin; CBS, cystathionine β-synthase; DHPR, dihydropteridine reductase; FAH, fumarylacetoacetate hydrolase; GNMT, glycine N-methyl transferase; 4-HPPD, 4-hydroxyphenylpyruvatedioxygenase; MAT I/III, methionine adenosyl transferase isoenzymes I/III; MSUD, maple syrup urine disease; PAH, phenylalanine hydroxylase; PKU, phenylketonuria; TAT, tyrosine aminotransferase.

Disorders targeted in the uniform screening panel are in **bold**.

- Prompt newborn screening is followed by a very narrow window of only a few days to confirm diagnosis and initiate treatment.
- Newborn screening and diagnostic testing
  - Elevated total level of leucine and isoleucine is reported as a positive result.
  - Diagnostic testing.
    - Plasma amino acid profile
    - Urine organic acid analysis
  - Branched-chain amino acids (BCAAs) and their keto acids are elevated.
  - Markers with the highest sensitivity for MSUD are elevated amino acid allo-isoleucine and increased leucine to alanine ratio.
- Management
  - Mainstay is dietary restriction of BCAA, while providing adequate amounts of the other amino acids and other nutrients.
    - Typically, a high-calorie, BCAA-free formula, in addition to a dietary source of whole protein (ie, standard infant formula or human milk).
    - Leucine must be rigorously restricted.
    - It may be necessary to supplement with isoleucine or valine.
  - Metabolic decompensations are typically triggered by infection, fasting, and dietary indiscretions.
    - Early symptoms include poor feeding, vomiting, and fever.
  - Dinitrophenylhydrazine urine testing for home detection of increasing BCAAs.
  - Altered level of consciousness and cerebral edema are a significant risk during episodes of illness.
    - Rapid treatment of increased intracranial pressure may prevent herniation.

- Early intervention significantly reduces neuropsychological deterioration over the long term.
- Liver transplantation is an option if disease is poorly controlled by diet.
  - Cannot reverse existing brain damage but will prevent overwhelming metabolic decompensation and further damage
- Sick day management.
  - Rapid elimination of accumulating leucine
  - Adequate calories to arrest protein breakdown
  - Control of brain edema/herniation

Elevated Methionine on Newborn Screen

- Homocystinuria and other disorders of transsulfuration and transmethylation.
- Methionine is the screening marker for cystathionine β-synthase (CBS) deficiency, the most prominent cause of homocystinuria.
- However, elevated methionine can be associated with other conditions (see **Table 1**).
  - Clinical characteristics
    - Eye (dislocated lens, myopia, glaucoma).
    - Bones (osteoporosis, lengthening of the long bones, scoliosis, high arched palate, pes cavus, widened metaphyses with spicules, long slender fingers, pectus deformities).
    - Central nervous system (intellectual disability, psychiatric disorders, seizures, dystonia).
    - Vascular (thrombus formation and thromboembolism).
    - Age at onset and severity are variable, even within a family.
      - Thromboembolism has been reported as early as infancy, but most features develop from later infancy to adolescence.
  - Newborn screening and diagnostic testing
    - Elevation of methionine on the newborn screen is reported as a positive result.
      - May also be elevated in tyrosinemia or other forms of liver disease
    - If newborn screen result is positive for hypermethioninemia, diagnostic testing includes
      - Plasma amino acid profile
      - Plasma total homocysteine
      - Vitamin B_{12} levels
      - Urine organic acid analysis
    - CBS deficiency will have hypermethioninemia and hyperhomocysteinemia.
    - Enzyme or molecular DNA assay are next steps.
    - Note that newborn screening will miss most of pyridoxine-responsive neonates who have CBS deficiency.
      - Clinical manifestations suggestive of CBS deficiency should trigger evaluation even if screening is typical.
    - Low methionine with elevated homocysteine should direct physician toward disorders of transmethylation (methylene tetrahydrofolate reductase and cobalamin complementation groups C-G deficiencies).
  - Management
    - Ascertain responsiveness to pyridoxine supplementation with a trial (probably done by the geneticist).
      - If responsive, pyridoxine supplementation alone is sufficient treatment.
      - If nonresponsive to pyridoxine, dietary methionine restriction and supplementation with L-cystine and betaine are recommended.
      - Methionine restriction and L-cystine supplementation have been shown to prevent intellectual disability, lens dislocation, and bony changes.
      - Betaine has been shown to reduce the incidence of thromboembolic events.
- Anticoagulant therapy has mixed results.
  - If neonate needs to undergo surgery, risk of thromboembolic events can be reduced by perioperative metabolic control and hydration.
  - Maternal CBS deficiency.
    - Hyperhomocysteinemia is associated with an increased risk of preeclampsia.
    - Women with CBS deficiency have an increased risk of thromboembolic events at baseline, which is further increased during the postpartum period.
    - Successful births have been reported with good metabolic control, which includes dietary methionine restriction, folate supplementation, and betaine for homocysteine reduction.

Elevated Tyrosine With Typical Phenylalanine on Newborn Screen

- Tyrosinemia (fumarylacetoacetate hydrolase [FAH] deficiency, tyrosine aminotransferase [TAT] deficiency, and transient tyrosinemia)

- Clinical characteristics
  - FAH deficiency is also called tyrosinemia type 1 or hepatorenal tyrosinemia.
    - Onset of biochemical changes typically occurs in the neonatal period or infancy.
    - Lethal if untreated.
    - Hepatic.
      - Elevated transaminases and coagulation abnormalities (elevated prothrombin time/partial thromboplastin time) are unresponsive to vitamin K.
      - Subsequent bleeding, hepatomegaly, and cirrhosis.
      - Can lead to hepatocellular carcinoma in childhood.
    - Renal.
      - Glomerular and tubular injury, with excessive renal loss of glucose, phosphate, amino acids, and bicarbonate (renal Fanconi syndrome)
      - Can lead to vitamin D unresponsive rickets, nephromegaly, and failure to thrive
    - Peripheral nerve pathologies.
      - Acute neuropathic pain
    - Hypertrophic cardiomyopathy, albeit rare, has been described.
  - TAT deficiency (tyrosinemia type 2 or oculocutaneous tyrosinemia).
    - Onset is typically in infancy.
    - Painful corneal erosions, circumcorneal injection, lacrimation, and photophobia.
      - Can mimic keratitis from herpes simplex infection, but lesions do not take up fluorescein dye.
    - Cutaneous lesions are painful, nonpruritic, hyperkeratotic scaly patches, typically localized to the palmoplantar regions.
      - Not hyperpigmented, distinguishing them from inflammatory skin conditions.
    - Half the neonates have intellectual disability.
  - Transient tyrosinemia caused by immaturity of the 4-hydroxyphenylpyruvate dioxygenase enzyme (and liver metabolism in general).
    - More prevalent in preterm neonates or those on high protein formula/intake (>5 g/kg/d).
    - Biochemical abnormality in an otherwise asymptomatic neonate.
    - Tyrosine level typically peaks by 2 weeks of age and resolves by 1 month or later in preterm neonates.
- Newborn screening and diagnostic testing
  - Elevated tyrosine level is reported as a positive result.
  - Succinylacetone (SA) is being added to state programs to identify neonates with tyrosinemia type 1 (FAH deficiency).
  - Diagnostic testing.
    - Plasma amino acid profile
    - Urine organic acid analysis
  - In all 3 enzyme deficiencies, tyrosine and its metabolites are elevated in plasma amino acid profile and urine organic acid analysis.
  - SA is elevated in FAH deficiency.
- Management
  - Check urine organic acids for SA.
  - Look for acquired causes of hepatocellular injury.
  - Mainstay of treatment is dietary restriction of tyrosine and phenylalanine by limiting natural protein.
    - Supplementation with a special formula and later medical foods devoid of tyrosine and phenylalanine
  - For FAH deficiency, 2-(2-nitro-4-trifluoromethylbenzoyl)-1,3-cyclohexanedione (NTBC) is used to prevent formation of the most toxic metabolites.
  - NTBC significantly reduces acute crises and chronic hepatic, renal, and peripheral neuropathic manifestations and dramatically lowers risk for hepatocellular carcinoma and neurocognitive delays.
  - Hepatic or combined hepatorenal transplantation can be curative.
  - For TAT deficiency, dietary intervention typically resolves the ocular and cutaneous symptoms.
    - A trial of pyridoxine can be considered.
  - Sick day management.
    - Most common presentations: acute hepatic crisis and acute peripheral neuropathy crisis.
    - First step: Limit catabolism with nutrition, preferably oral if tolerated, or else lavage.
    - Supplemental intravenous (IV) glucose.
    - Treat infection.
    - Further evaluation and supportive management depending on affected system.

- Maternal tyrosinemia type 1.
  - Successful pregnancy outcomes have been reported.
  - NTBC is not teratogenic, and continued use during pregnancy is recommended.
  - Screening result in neonates will be positive for elevated tyrosine, secondary to maternal tyrosinemia and NTBC treatment; however, this spontaneously resolves.
  - Urine organic acid analysis result will be negative for SA in these neonates.

Elevated Citrulline on Newborn Screen

- A marker of 2 urea cycle disorders (citrullinemia and argininosuccinic aciduria)
- Clinical characteristics
  - Both conditions affect urea cycle with similar clinical picture.
  - Onset varies from the early neonatal period to late adulthood, depending on degree of enzyme deficiency.
  - Both lead to hyperammonemia, a respiratory center stimulant.
    - Tachypnea (and associated respiratory alkalosis), respiratory depression, apnea (and acidosis).
    - Diffuse cerebral edema, a bulging fontanel, rapid increase in head circumference (in neonates), vomiting, lethargy, hypothermia, poor feeding, and, eventually, coma and death.
    - Hyperammonemia is often confused with sepsis, cerebral trauma, or intracranial bleeding.
  - Intellectual disability may occur even with good treatment.
  - Neonates with argininosuccinic aciduria may have hair that breaks easily and has a characteristic microscopic appearance, with periodic bulging of hair shafts and rupture of the cortical sheath (trichorrhexis nodosa or bamboo hair).
  - Neonatal onset with severe enzyme deficiency typically occurs ≥24 hours after birth.
  - Hyperammonemia occurring earlier may be the result of transient hyperammonemia of the newborn, pyruvate dehydrogenase deficiency, glutaric acidemia (GA) type 2, or sepsis.
  - Late onset in neonates with a less severe enzyme deficiency may be triggered by
    - Increase in protein intake
    - Infection or other stressors
  - Late onset clinical features similar to neonatal, but milder and intermittent.
  - Neonates with hyperammonemia or other protein intolerance not identified with screening or illness may self-select a low protein diet, an important cue in the history.
- Newborn screening and diagnostic testing
  - Elevated citrulline is reported as a positive result.
    - Further testing is required to define the cause.
  - Diagnostic testing includes plasma ammonia, plasma amino acid profile, and urine organic acid analysis.
    - Ammonia (and, if possible, the other 2 tests) must be obtained at the earliest possible opportunity.
    - Hyperammonemia and plasma amino acid profile with increased glutamine and alanine, and relatively low arginine and ornithine, are present in all 4 urea cycle defects (carbamoyl phosphate synthetase, ornithine transcarbamylase, argininosuccinate synthetase [AS], and argininosuccinate lyase [AL] deficiencies).
    - Increased citrulline is only seen in AS and AL deficiencies.
    - When citrulline is significantly elevated, and argininosuccinic acid is not, AS deficiency (citrullinemia type 1) is diagnosed.
    - If argininosuccinic acid is also increased, AL deficiency (argininosuccinic acidemia) is diagnosed.
- Management
  - Mainstay is dietary protein restriction and supplementation with a protein-free caloric powder (containing carbohydrates, lipids, minerals, trace elements, and vitamins) and arginine.
  - Neonates with AS deficiency are given phenylbutyrate (a precursor of phenylacetate) to enhance excretion of excess nitrogen as phenylacetylglutamine.
    - Not usually required for neonates with AL deficiency.
    - Sodium benzoate is sometimes also used.
  - Long-term treatment control and compliance is assessed by monitoring plasma glutamine (which may be elevated even when ammonia is normal) in the plasma amino acids.
  - Liver transplantation may be considered for severe cases if metabolic control is difficult to achieve or if high risk for catastrophic hyperammonemic event.

- Sick day management.
  - In case of respiratory symptoms or encephalopathy, assess degree of hyperammonemia.
  - If significant elevation, discontinue all protein and initiate IV 10% glucose at maintenance.
  - Urgent hemodialysis is best to lower plasma ammonia, but high-flow hemofiltration has been used.
    - Repeat until plasma ammonia level is down to 3× upper reference range.
    - Then treat with IV sodium benzoate and sodium phenylacetate (in citrullinemia) and 10% arginine (in citrullinemia or argininosuccinic acidemia) in 10% dextrose.
    - IV ondansetron 0.15 mg/kg during first 15 minutes of initial infusion can help with vomiting.
    - Increased intracranial pressure can be managed with mannitol.
    - Once ammonia levels are near reference range, IV medications can be switched to oral.

Results Suggesting Mitochondrial Fatty Acid Oxidation Disorders

- Mitochondrial fatty acid oxidation enzyme analytes and follow-up diagnostic testing are summarized in **Table 2.**
- Clinical characteristics.
  - Onset can vary from day 1 of life into adulthood.
  - Episodes of altered mental status, lethargy, seizures, vomiting, dyspnea, tachypnea, apnea, and coma, triggered by catabolic stressors.
    - Presentation is often confused with sepsis.
    - If severe, can cause significant neurodevelopmental delays.
  - Fatty infiltration of the liver can lead to hepatomegaly, liver dysfunction, and associated complications.
    - Cerebrohepatic involvement is often confused with Reye syndrome.
  - Families can have a history of previous loss from unknown causes or sudden infant death syndrome.
  - Recessive conditions; therefore, unscreened siblings of affected neonates should be tested.
  - Carnitine uptake defect, very long-chain acyl-CoA (coenzyme A) dehydrogenase (VLCAD), long-chain 3-hydroxyacyl-CoA dehydrogenase (LCHAD), and trifunctional protein (TFP) deficiencies can present with cardiomyopathy and skeletal myopathy, causing exercise intolerance, weakness, soreness, fatigue, or rhabdomyolysis.
    - Rare in medium-chain acyl-CoA dehydrogenase (MCAD) deficiency

Table 2. Mitochondrial Fatty Acid Oxidation Disorders

Abnormal Levels of Carnitine and Acylcarnitines on Newborn Screen	Possible Disorders	Diagnostic Testing
Low/absent free carnitine	**CUD**, also called carnitine transporter	Plasma and urine total and free carnitine (and plasma creatinine, for determining the fractional excretion of carnitine)
Elevated C8 ± C6 and C10	**MCAD**	Plasma acylcarnitine profile, urine organic acid analysis, urine acylglycine analysis
Elevated C14:1	**VLCAD**	Plasma acylcarnitine profile, urine organic acid analysis
Elevated C16-OH ± C18-OH	**LCHAD, TFP deficiency**	Plasma acylcarnitine profile, urine organic acid analysis

Abbreviations: :1, presence of one double bond; C, carbon length; CUD, carnitine uptake defect; LCHAD, long-chain 3-hydroxyacyl-CoA dehydrogenase; MCAD, medium-chain acyl-CoA dehydrogenase; OH, hydroxy fatty acid; TFP, trifunctional protein; VLCAD, very long-chain acyl-CoA dehydrogenase.

Disorders targeted in the uniform screening panel are in **bold**.

- Carnitine uptake defect (CUD).
  - First peak is between 3 months and 2½ years of age, presenting as episodes of hypoketotic hypoglycemia.
    - If recurrent, fatty infiltration of major organs can be seen.
  - Second peak is between 1 and 7 years of age, presenting as a cardiomyopathy.
- MCAD deficiency.
  - The most common mitochondrial fatty acid oxidation disorder, with wide clinical variability ranging from neonatal death to absence of symptoms into adulthood.
  - Rarely, a parent of a child with MCAD deficiency is also detected to have MCAD deficiency.
- VLCAD deficiency.
  - Categorized as 2 distinct phenotypes, distinguished by enzyme activity or mutation analysis
  - Early-onset, more severe VLCAD cardiomyopathy
  - Later-onset, less severe VLCAD hypoglycemia/hepatic
- LCHAD/TFP deficiency.
  - Possible in addition to the common manifestations previously listed.
    - Pigmentary retinopathy and mixed neuropathy
    - Hemolytic anemia and thrombocytopenia
  - Women carrying a fetus affected with LCHAD/TFP deficiency may have acute fatty liver of pregnancy or HELLP (**h**emolysis, **e**levated **l**iver enzymes, **l**ow **p**latelets) syndrome.

■ Newborn screening and diagnostic testing.
- Each of the following 4 screened disorders has a specific pattern of acylcarnitine abnormalities:
  - CUD: low/absent free carnitine ± low levels of all acylcarnitine species
  - MCAD deficiency: elevated C8 ± elevated C6 and C10 acylcarnitine species
  - VLCAD deficiency: elevated C14:1 ± other long-chain acylcarnitine species
  - LCHAD/TFP deficiency: elevated C16-OH ± C18-OH and other long-chain acylcarnitine species
- Diagnostic testing.
  - Plasma acylcarnitine profile
  - Urine organic acid analysis
  - Urine acylglycine analysis if screening result is positive for C8 ± C6 and C10
- Common mutation analysis (MCAD, LCHAD) or gene sequencing assays are the next steps.
- Maternal CUD and other mitochondrial fatty acid oxidation disorders.
  - If diagnostic testing for CUD in a neonate whose screening result is positive is typical, one must rule out a primary or secondary carnitine deficiency in the mother, including CUD or deficiencies of MCAD, 3-methylcrotonyl-CoA (3-MCC) carboxylase, or glutaryl-CoA dehydrogenase.
  - Others are usually asymptomatic.

■ Management.
- Mainstay of daily management for all types is to avoid fasting and provide adequate calories intravenously during episodes of diminished oral intake.
- CUD: carnitine supplementation.
  - Very large amounts may be required.
  - Most common side effects are loose stools and a fishy odor.
- MCAD deficiency: moderate restriction of dietary fat ("heart-healthy diet") and carnitine supplementation.
- LCHAD and VLCAD deficiency: Restrict long-chain fat intake, providing adequate amounts of essential long-chain fatty acids.
  - Medium-chain triglyceride formula or supplement will provide fatty acids of medium-chain length, which can be oxidized for energy.
- In older children, uncooked cornstarch can provide a gradual steady source of complex carbohydrates overnight, avoiding the fasting state associated with overnight sleep.
- Patients with LCHAD/TFP deficiency should undergo regular ophthalmology evaluations.
- Sick day management.
  - Goal: Divert metabolism away from affected mitochondrial fatty acid oxidation pathway and provide carnitine to aid excretion of toxic metabolic intermediates.
  - Anticipatory treatment with D10 1/4NS at 1.5–2× maintenance with carnitine supplementation at first sign of illness.
  - Assess degree of metabolic derangement with basic metabolic panel, ammonia, uric acid, creatine phosphokinase, lactate, liver function tests, complete blood cell count, urinalysis, plasma total and free carnitine, acylcarnitine profile, and urine organic acid analysis (plus urine acylglycine analysis in MCAD deficiency).

Results Suggesting Organic Acid Disorders

- Many features of organic acidemia can be explained by accumulation of toxic organic acid intermediates.
  - Thus, most of the organic acidemia discussed as follows have hyperketotic hypoglycemia, metabolic acidosis, and hyperammonemia presenting as an encephalopathy (poor feeding, vomiting, lethargy, seizures, coma) with signs of metabolic acidosis (hyperpnea).
  - Primary goal of therapy is to minimize pathway use with the deficient enzyme.
    - Limiting dietary intake of its precursor
    - Suppressing production of the substrate from endogenous sources
    - Enhancing alternative pathways of utilization and detoxification
  - Dietary limitation must maintain a "balanced" caloric intake with "substrate-free" formula supplementation.
    - The body will still generate some of the targeted substrate endogenously, exacerbated in times of catabolic stress (eg, poor intake, infection, illness, fever, trauma).
    - Adequate calories suppress lipolysis, ketogenesis, and gluconeogenesis.
    - Free CoA is recovered from the substrate at the metabolic block using alternative pathways.
    - Carnitine, a carrier molecule for fatty acid transfer into the mitochondria, is especially helpful for conjugation with other substances that have CoA intermediates.
    - Occasionally, a vitamin cofactor for the deficient enzyme can boost its catalytic ability.
- Mild, brief illnesses are generally treated by removing specific substrate from the daily oral intake for 1–2 days and providing adequate calories (sick day formula).
  - Supplemental carnitine or other detoxifying agents may be given.
- If oral treatment is precluded, IV glucose (with appropriate electrolytes) and lipids are used.
- In acute crisis (eg, hyperketotic hypoglycemia, metabolic acidosis, hyperammonemia), additional measures must be taken.
  - Caloric support.
  - IV L-carnitine.
  - Hemodialysis or hemofiltration for severe hyperammonemia.
  - Monitor for blood glucose, ketones, ammonia, and other metabolites, and cerebral perfusion and edema.
- Prolonged complete avoidance of an essential nutrient will lead to ongoing catabolism.
- Critically ill patients are usually best treated in an intensive care unit with rapid metabolic analysis available on-site.
- **Table 3** summarizes the analytes screened for and the follow-up diagnostic testing for organic acid disorders.

Elevated C3 (Propionylcarnitine) Species on Newborn Screen

- Propionic acidemia/methylmalonic acidemia/some disorders of vitamin B_{12} metabolism
  - Clinical characteristics
    - Onset of symptoms can range from infancy to adulthood, based on the severity of the enzyme deficiency.
    - Common clinical manifestations include vomiting, poor feeding, lethargy, and tachypnea.
    - In milder cases, self-selected protein avoidance.
    - Late complications include cognitive delays, seizures, dystonia, and poor growth.
    - Cardiomyopathy later in life with propionic acidemia; can be the presenting feature.
    - Chronic renal disease and failure frequently occur in methylmalonic acidemia.
    - Some disorders of vitamin B_{12} metabolism present similar to methylmalonic acidemia.
    - Neonates with some vitamin B_{12} metabolism disorders have homocystinuria, which puts them at an increased risk for thrombosis and retinopathy.
    - These disorders are unrelated to nonketotic hyperglycinemia, a disorder of glycine cleavage.
  - Newborn screening and diagnostic testing
    - Elevation of C3 acylcarnitine species (propionylcarnitine) on newborn screening can indicate propionic or methylmalonic acidemia.
    - Diagnostic testing to help differentiate among propionic acidemia, methylmalonic acidemia (mut0, mut-, CblA, CblB deficiency), cobalamin transport, metabolism disorders (CblC, CblD, CbF deficiency), and vitamin B_{12} deficiency (caused by maternal deficiency).
      - Plasma acylcarnitine profile
      - Total homocysteine
        - Elevated total plasma homocysteine strongly suggests a disorder of cobalamin availability, transport, or metabolism.
      - Urine organic acid analysis

Table 3. Organic Acid Disorders

Elevated Acylcarnitine Analytes on Newborn Screen	Possible Disorders	Diagnostic Testing
C3 (propionylcarnitine)	**Propionyl-CoA carboxylase deficiency (propionic acidemia), methylmalonyl-CoA mutase deficiency (methylmalonic acidemia), cobalamin metabolism disorders**, maternal vitamin B_{12} deficiency	Plasma acylcarnitine, profile, total plasma homocysteine, urine organic acid analysis
C5	**Isovaleryl-CoA dehydrogenase deficiency (isovaleric acidemia)**, antibiotics containing pivalic acid	Plasma acylcarnitine profile, urine organic acid analysis, urine acylglycine analysis
C5-DC (glutarylcarnitine)	**Glutaryl-CoA dehydrogenase deficiency (glutaric acidemia type 1)**	Plasma acylcarnitine profile, urine organic acid analysis, urine acylglycine analysis
C5-OH	**3-MCCC deficiency**, **HMG-CoA lyase deficiency, multiple carboxylase (holocarboxylase synthetase) deficiency,** biotinidase deficiency, **mitochondrial acetoacetyl-CoA carboxylase (branched chain ketothiolase) deficiency**	Plasma acylcarnitine profile, urine organic acid analysis

Abbreviations: 3-MCCC, 3-methylcrotonyl-CoA carboxylase; C, carbon length; CoA, coenzyme A; DC, dicarboxylic; HMG-CoA, 3-hydroxy-3-methylglutaryl-CoA lyase; OH, hydroxy.

Disorders targeted in the uniform screening panel are in **bold**.

  - Complementation group analysis, enzyme assays, or mutation analysis are the next steps.
  - Elevation of the C3 acylcarnitine species on newborn screening indicates a possible problem in this metabolic pathway.
  - Propionic acidemia can be secondary to deficiency of propionyl CoA carboxylase or its cofactor, biotin.
- Management
  - Limit natural protein to the amount required or tolerated of the toxic amino acids.
  - Supplement with special formula devoid of toxic amino acids.
  - Provide adequate calories.
  - Carnitine supplementation is essential in propionic acidemia.
    - In methylmalonic acidemia, relatively little carnitine is lost.
  - Chronic alkali therapy is sometimes needed.
  - Gut production of propionate can be reduced with pulsed oral administration of broad-spectrum antibiotics and early treatment of constipation.
  - Neonates with cobalamin transport and metabolic defects (CblA and CblB) usually respond to hydroxocobalamin given by daily injection.
  - Betaine, carnitine, folic acid, and pyridoxine are also used.
  - In neonates with frequent metabolic decompensation despite medical management, hepatic or hepatorenal transplantation significantly reduces decompensation frequency.
  - Valproate should be avoided.
  - All nephrotoxic drugs should be used cautiously in infants with methylmalonic acidemia.

- Sick day management.
  - Confirm acute metabolic decompensation with plasma electrolytes, blood gases, and ammonia; lactate and complete blood cell count will show lactic acidosis and cytopenia.
  - If abnormal, obtain plasma acylcarnitine profile and urine organic acid analysis and orotic acid without delaying treatment.
  - Discontinue all protein for first 24–48 hours.
  - IV fluids with dextrose ≥10%.
  - Double daily dose of carnitine.
  - Initiate sodium benzoate and carbamylglutamate or, if severe, continuous hemofiltration.
  - Do not use phenylbutyrate or phenylacetate.
  - Sodium bicarbonate might be required if acidosis is not controlled.
  - See the consensus management guidelines published in 2014 by Baumgartner and colleagues, which provide detailed dosing recommendations for glucose, hydroxocobalamin, biotin, sodium benzoate, and sodium phenylbutyrate, L-arginine-HCL, and N-carbamyl-glutamate therapies.

Elevated C5 Acylcarnitine Species on Newborn Screen

- Isovaleric acidemia
  - Clinical characteristics
    - Onset is typically in the neonatal period with episodes of vomiting, poor feeding, lethargy, metabolic stroke, and coma (encephalopathy), triggered by catabolic stressors.
    - Peculiar odor reminiscent of sweaty feet.
    - Transient pancytopenia caused by bone marrow suppression.
    - Long-term complications include neuro-cognitive delays and failure to thrive, if untreated.
    - Good neurocognitive outcome is possible for milder cases.
    - Pancreatitis, rarely.
  - Newborn screening and diagnostic testing
    - Elevated C5 acylcarnitine is reported as a positive result.
    - Newborn screening can detect C5 acylcarnitine species using MS/MS but cannot distinguish the different C5 isomers seen in other organic acidemia and certain antibiotic use.
    - Diagnostic testing.
      - Quantitative plasma acylcarnitine profile
      - Urine organic acid
      - Urine acylglycine analysis
    - Enzyme or DNA molecular assays are the next steps.
    - In isovaleric acidemia, a specific mutation, 932C>T, has been described with a milder biochemical phenotype.
      - Neonates with ≥1 copy of this mutation tend to be asymptomatic or have a milder clinical picture.
  - Management
    - Mainstay is limitation of dietary leucine by restricting natural protein to the amount required or tolerated.
    - Supplementation with special formula devoid of leucine.
    - Provision of adequate calories.
    - Carnitine or glycine supplementation enhances excretion of the toxic organic acid intermediates.
    - Good neurocognitive outcome is possible in many cases.
    - Sick day management.
      - Remove leucine from diet and increase total caloric intake with simple sugars and leucine-free formula.
      - If unable to tolerate oral feeding, IV glucose at 8 mg/kg/min (with insulin as needed) to maintain euglycemia.
      - Reintroduce leucine and other amino acids after 24 hours to avoid protein catabolism.
      - Carnitine and glycine supplementation should be continued.
  - Maternal isovaleric acidemia
    - Good metabolic control using management as during nonpregnant states can result in successful pregnancy outcome.

Elevated C5-DC (Glutarylcarnitine) Acylcarnitine Species on Newborn Screen

- GA type 1
  - Clinical characteristics
    - Most neonates are normal at birth, except for macrocephaly and occasional nonspecific findings of jitteriness and irritability.
    - Brain magnetic resonance imaging may show macrocephaly, increased fluid over the cerebral hemispheres; sylvian fissure may be widely open.

- Onset of symptoms (provoked by catabolic stressors) is typically between 6 and 18 months of age.
  - Vomiting, hypotonia, developmental regression, seizures, dystonia, dyskinesis (facial grimacing, tongue thrusting, fisting, opisthotonus), and coma (encephalopathy).
  - Hepatomegaly might be present.
  - Most neonates do not fully recover from these acute episodes.
  - Neurodegenerative changes accumulate with each new episode, with frontotemporal atrophy and striatal degeneration.
  - Cognition and intellect are not affected.
  - Acute pancreatitis has been reported in association with GA type 1.

- Newborn screening and diagnostic testing
  - Elevated C5-DC (glutarylcarnitine) acylcarnitine using MS/MS is reported as a positive result.
  - Diagnostic testing.
    - Quantitative plasma amino acid profile
    - Urine organic acid
    - Urine acylglycine analysis
    - Elevated glutaric and hydroxyglutaric species in neonates with this enzyme deficiency
  - Enzyme and molecular DNA assays are the next steps.
- Management
  - The possibility of neurodegeneration can be reduced with dietary limitation of lysine intake by natural/tolerated level of the toxic amino acids.
  - Supplementation with special formula devoid of the toxic amino acids.
  - Provision of adequate calories.
  - Carnitine supplementation.
  - Aggressive intervention during catabolic stresses.
  - Sick day management.
    - Increased fluid and caloric intake with glucose (plus insulin if needed)
    - Complete removal of all natural protein for 24–48 hours
    - Carnitine supplementation

- Isolated 3-MCC deficiency
  - Clinical characteristics
    - Onset typically includes illness in neonatal period with episodes of vomiting, lethargy, hypotonia, seizures, metabolic stroke, and coma (encephalopathy) triggered by catabolic stressors.
    - Cardiomyopathy on presentation in some neonates.
    - Neonates may have a peculiar odor reminiscent of cat urine.
    - Long-term complications include failure to thrive and neurocognitive delays.
      - Emerging data suggest <10% of neonates with 3-MCC deficiency actually develop these symptoms.
  - Newborn screening and diagnostic testing
    - Elevated C5-OH acylcarnitine is reported as a positive result.
    - MS/MS detects C5-OH acylcarnitine species but cannot distinguish different C5-OH isomers.
    - Diagnostic/confirmatory testing.
      - Quantitative plasma acylcarnitine
      - Urine organic acid analysis
    - Enzyme or molecular DNA analysis is the next step.
  - Management
    - Most neonates are asymptomatic except during times of stress.
    - Lifelong dietary protein (leucine) restriction and carnitine or glycine supplementation are usually not necessary.
    - Sick day management.
      - For patients who become asymptomatic during catabolic stress: Increase total caloric intake enterally or parenterally.
      - Carnitine and glycine supplementation.
    - Positive newborn screening result for 3-MCC deficiency is sometimes caused by maternal enzyme deficiency; mothers with this condition often are asymptomatic.
- 3-hydroxy-3-methylglutaryl-CoA lyase (HMG-CoA lyase) deficiency
  - Clinical characteristics
    - Onset can be in the neonatal period to late childhood.
    - Episodes of vomiting, lethargy, hypotonia, seizures, and coma (acute encephalopathy), triggered by catabolic stressors.

- Unlike in isovaleryl-CoA dehydrogenase and 3-MCC deficiencies, ketosis is not prominent.
- Differential diagnosis for nonketotic or hypoketotic hypoglycemia includes HMG-CoA lyase deficiency, acetoacetyl-CoA thiolase deficiency, and mitochondrial fatty acid oxidation disorders.
- Long-term complications include neurocognitive delays and seizures secondary to leukodystrophic insults during acute episodes.
- Isolated cases of cardiomyopathy and pancreatitis.

- Newborn screening and diagnostic testing
  - Elevated C5-OH acylcarnitine on newborn screening is reported as a positive result.
  - Newborn screening can detect C5-OH acylcarnitine species using MS/MS but cannot distinguish the different C5-OH isomers.
  - Diagnostic/confirmatory testing.
    - Quantitative plasma acylcarnitine profile
    - Urine organic acid analysis
  - Enzyme or molecular DNA analysis is the next step.
- Management
  - The possibility of neurodegeneration can be reduced with
    - Dietary limitation of lysine intake through natural/tolerated level of toxic amino acids
    - Supplementation with special formula devoid of toxic amino acids
    - Provision of adequate calories
    - Carnitine supplementation
    - Aggressive intervention during catabolic stresses
  - Sick day management
    - Increase total caloric intake, enterally or parenterally
    - Carnitine supplementation

■ Multiple carboxylase deficiency
- Clinical characteristics
  - Onset typically in the first 3 months of age.
  - Poor feeding, hypotonia, lethargy, seizures, and developmental delays.
  - Dermatitis, alopecia, and immune dysfunction with frequent infections can be present.
  - Deficiency of holocarboxylase synthetase can lead to deficiency of ≥1 carboxylases, presenting as a multiple carboxylase deficiency.
- Newborn screening and diagnostic testing
  - Elevation of C5-OH acylcarnitine is reported as a positive result.
  - Newborn screening using MS/MS will detect C5-OH acylcarnitine species but cannot distinguish among the different C5-OH isomers.
  - Diagnostic testing.
    - Quantitative plasma acylcarnitine profile.
    - Urine organic acid analysis.
    - Gene sequencing for the holocarboxylase synthetase gene is typically not required, except in neonates who do not respond to standard treatment, including supplemental biotin.
- Management
  - Neonates whose newborn screening results are positive or symptomatic must be seen immediately by the primary care pediatrician.
  - All neonates with positive results should be started empirically on 10 mg of oral biotin (free, not bound) daily.
  - Most neonates respond to biotin supplementation; occasionally, some neonates do not.
  - No other treatment is currently available.

■ Mitochondrial acetoacetyl-CoA thiolase (branched chain ketothiolase) deficiency
- Clinical characteristics
  - Onset typically in the first 2 years of life
  - Episodes of vomiting, lethargy, and coma (encephalopathy), triggered by catabolic stressors
- Newborn screening and diagnostic testing
  - Elevation of C5-OH acylcarnitine on newborn screening is reported as a positive result.
  - Newborn screening MS/MS cannot distinguish the different C5-OH isomers.
  - Diagnostic testing.
    - Quantitative plasma acylcarnitine profile.
    - Urine organic acid analysis.
    - Enzyme or mutation analysis can confirm diagnosis.
- Management
  - Mainstay is to avoid fasting.
  - Dietary restriction of protein, but not fat intake, is recommended.
  - Carnitine supplementation can be considered.
  - Ketogenic diet is contraindicated.

Screening for Lead Poisoning

BACKGROUND

- Lead adversely affects
  - Neurocognition and neurodevelopment
    - Attention, vigilance, language development, the transfer of information from short-term to long-term memory
  - Behavior
    - Antisocial, aggressive tendencies
- Negative effects are seen at levels >10 mcg/dL.
- The Centers for Disease Control and Prevention (CDC) now defines a blood lead level that is at the 97.5th percentile, currently 5 mcg/dL, as elevated.
- Levels vary inversely with family income.
  - An impoverished home and Medicaid enrollment are closely linked to increased exposure.
  - Universal screening of children on Medicaid between 9 and 12 months and at 2 years of age has been required.
- Lead-contaminated interior or exterior household paint that is peeling or chipping is the most common, concentrated source of exposure.
  - The older a house, the more likely it is to contain lead-based paint.
  - The less affluent the family, the more likely the paint is to be in disrepair.
  - Housing built before 1950 poses the greatest danger.
    - 50% of these houses are in California, Illinois, Massachusetts, Missouri, New York, Ohio, and Pennsylvania.
- Other sources of lead exposure include
  - Water
  - Food
  - Soil
  - Toys
  - Ceramics
  - Parents whose clothing becomes contaminated with lead at work
    - Battery production or repair
    - Pottery making
    - Smelting
    - Printing
    - Paint contracting
    - Working on a firing range
    - Brass foundry
    - Demolition or renovation of outdoor structures
  - Hobbies
    - Making lead fishing sinkers or bullets
    - Collecting lead figurines
    - Spending time at indoor firing ranges
    - Making pottery
  - Home remedies (in certain Latin American and Southeast Asian cultures): azarcon or greta
  - Cosmetics: kohl
  - Lead plumbing, especially in areas with older water supplies

GOALS

- Prevention of severe toxicity and deaths, eg, due to accidental ingestion of lead-containing necklaces and metallic charms
- Reduction of low-level effects through community abatement and clinical screening
  - Each 10 mcg/dL increase in blood lead results in a loss of 2–3 points in IQ.

GENERAL APPROACH

- CDC guidance defines national standards for screening programs.
  - The CDC recommends use of venous or capillary blood lead level as the examination of choice.
    - Capillary specimens collected by finger stick are acceptable, but values ≥10 mcg/dL must be confirmed with a venous sample.
  - 10 mcg/dL is used as the cutoff point for defining an elevated lead level.
  - Allowable error (per Clinical Laboratory Improvement Amendments) is ±4 mcg/dL or 10% of the value, whichever is greater.
  - At low levels, the allowable laboratory error can result in misclassification that might affect management.
- The CDC advises state health officials to develop screening programs based on risk characteristics of their local communities.
- The CDC advises professionals to use blood lead tests to screen[1]
  - 1- and 2-year-olds (and 3- to 6-year-olds who have not been screened previously) who meet ≥1 of the following criteria:
    - A child whose parents are concerned that the child may have been exposed
    - A child who lives in or regularly visits a house with peeling or chipping paint built before 1980
    - A child who lives in or regularly visits a house with recent or ongoing renovation or remodeling
    - A child who has a sibling or a playmate with an elevated blood lead level

  - A child who lives with an adult whose job or hobby involves exposure to lead
  - A child who lives near an active lead smelter, battery recycling plant, or other industry likely to release lead
  - A child who is a recent immigrant, refugee, or foreign adoptee
  - A child who has a household member who uses traditional, folk, or ethnic remedies or cosmetics or who routinely eats food imported informally (eg, by a family member) from abroad
  - A child who has recently immigrated to the United States or who has been internationally adopted
- If, at the 2-year screen, the blood lead level is again <10 mcg/dL and the child's potential exposures have not increased, further screening is not necessary.

- In communities where universal screening is recommended, children whose blood lead screening test result at age 1 year is <10 mcg/dL should be rescreened at age 2 years.
- Screening by questionnaire to evaluate risk.
  - Part of the CDC guidelines but limited by variable sensitivity and specificity
  - Still used by some states and localities as part of an overall lead-screening strategy, often with modifications in the specific questions used based on locale
- In addition to state- or local-level guidelines, health care professionals should watch for children who should be screened because of exposure to less usual sources of lead from parental occupations or hobbies.
- If parents or health care professionals suspect lead exposure, promptly test for blood lead, regardless of
  - Patient age
  - General health department recommendations
  - Responses to screening questionnaires
- Health care professionals must participate in and comply with the recommended program.
  - Compliance needs to be improved, especially for at-risk children.
- The CDC Web site has the latest, most accurate screening questions by region.

SPECIFIC INTERVENTIONS

CDC Recommended Test Schedule for Follow-up of Positive Screen Results

- See **Table 1.**

Management by Blood Level Results

- The CDC recommends that any blood lead value that is at or above the reference value of 5 mcg/dL and <10 mcg/dL should be confirmed within 1–3 months, and this should be ongoing until the level comes down to <5 mcg/dL.

Table 1. Recommended Schedule for Obtaining a Confirmatory Venous Sample

Screening Test Result (mcg/dL)	Recommendation for Confirmation Testing
5–<10	Confirm with a venous lead level, within 1–3 months if possible; this should be ongoing until the level is <5 mcg/dL.
10–44	Confirm the blood lead level with a venous sample within 1–3 months for those children with a blood lead level of 10–24 mcg/dL and within 2 weeks–1 month for those children with a blood lead level of 25–44 mcg/dL. Repeat confirmations at the same intervals until blood lead levels decline (ie, for children with repeat blood lead levels of 25–44 mcg/dL). Repeat the blood lead test at 2 weeks–1 month intervals until it is in the range of 5–24 mcg/dL, at which time blood lead testing should be repeated at 1–3 month intervals until it is below 5 mcg/dL.

The higher the blood lead level on the screening test, the more urgent will be the need for confirmatory testing.

Adapted from Centers for Disease Control and Prevention. *Screening Young Children for Lead Poisoning: Guidance for State and Local Public Health Officials.* Atlanta, GA: US Department of Health and Human Services; 1997.

- Blood lead values ≥10 mcg/dL should be confirmed as follows:
  - 10–24 mcg/dL: Confirm within 1–3 months.
  - 25–44 mcg/dL: Confirm within 2 weeks–1 month.
  - 45–69 mcg/dL: Confirm within 48 hours.
  - Patients with blood lead values ≥70 mcg/dL should be treated emergently and have their blood lead levels retested.
- Blood lead values of 10–19 mcg/dL.
  - All children with blood lead levels ≥5 mcg/dL are encouraged to have ongoing monitoring for continuing lead finger-stick blood test, confirmed with a venous blood lead test.
  - All children with venous blood lead levels ≥5 mcg/dL are recommended by the CDC to receive medical and environmental evaluations and counseling. The evaluation consists of
    - Detailed medical, nutritional, developmental, and environmental history and a complete physical examination.
    - Laboratory evaluation of iron status, including hematocrit and mean corpuscular volume. Those with a low hematocrit or low mean corpuscular volume should be tested with a ferritin level or iron and iron-binding capacity levels to identify iron deficiency.
    - Environmental history to identify potential sources of the child's exposure, such as living in or visiting a home built before 1950 or one built between 1950 and 1978.
  - Nutritional assessment to identify eating patterns that result in increased absorption of lead from the gastrointestinal tract (eg, iron deficiency, low calcium intake, infrequent meals).
    - Many children are eligible for support from Women, Infants, and Children and should be referred.
    - If the child is iron deficient, iron supplements should be prescribed.
    - Increasing calcium intake is not proven but generally recommended, especially when calcium intake is low.
    - Increasing meal frequency may decrease lead absorption but should be done in the context of a diet not excessive in calories.
- Blood lead values 20–44 mcg/dL.
  - Families should be counseled to
    - Have lead-based paint abatement performed by a properly licensed contractor and, if possible, with supervision of the local health department.
    - Relocate children and pregnant women to another site while abatement is being performed.
    - Thoroughly remove dust before allowing children to reinhabit the home.
- Blood lead values ≥45 mcg/dL.
  - Remove from sources of lead.
  - Initiate chelation therapy.
  - Refer to a pediatrician who is familiar with the pharmacologic management of childhood lead poisoning.
  - Effects of succimer when used in more prolonged or repeated treatment courses requires further study.

How to Avoid Lead Hazards in the Home

- Cover chipping or peeling leaded paint.
- Move cribs, playpens, furniture, and play areas away from chipping or peeling paint.
- Wet-mop floors and wet-clean windowsills and window wells with a high-phosphate detergent.
- Avoid dry dusting or sweeping.
- Wash children's hands, toys, and pacifiers regularly.
- Use cold water for cooking; run tap water for 2–3 minutes every morning before using.
- Repair deteriorated windowpanes in house and on porches.
- Replace old windows.
- Remove paint in old homes (only by trained contractors).
- Post-abatement cleanup, preferably by professional housecleaners, is essential.
- Relocate the family to lead-safe housing.

REFERENCE

1. From Centers for Disease Control and Prevention. Recommendations for blood lead screening of Medicaid-eligible children aged 1-5 years: an updated approach to targeting a group at high risk. *MMWR Morb Mortal Wkly Rep.* 2009;58(RR09):1–11

DEFINITION

- *Scrotal swelling* is usually classified as
  - Painful versus painless
  - Acute versus chronic
- *Testicular torsion* is the twisting of the spermatic cord, with resulting compromise of the blood supply to the testis.
  - The appendix testis is a vestige of the müllerian (paramesonephric) duct system that hangs from the anterior surface of the testis where it meets the head of the epididymis and is susceptible to torsion.
- *Epididymitis* is inflammation of the epididymis.
- *Orchitis* is inflammation of the testis.
- *Inguinal hernias* and *hydroceles* fall along a continuum, both caused by persistent patency of the processus vaginalis.
- *Varicoceles* are dilations of the spermatic veins or pampiniform plexus.
- *Spermatoceles* and *epididymal cysts* are sperm-filled cystic lesions attached to the anterior surface of the testis.

HISTORY

- Take the history from the child (when possible) and parent.
  - Familial tendency to torsion has been described.
- Determine
  - Whether swelling or pain is a single event or recurrent
  - Whether swelling or pain is acute or chronic
  - Exact timing of the onset of symptoms, particularly in the presence of acute pain and swelling
    - Acute testicular torsion may have a predilection for the colder months.
- Nature of the pain.
  - Sharp
  - Dull
  - Constant
  - Intermittent
  - Constant, with intermittent increases in intensity
  - Associated with nausea or vomiting
- Location of pain.
  - Scrotum, specifically the testis
  - Radiation into abdomen or from abdomen into the scrotum
- Laterality of swelling and pain.
- Activity or positions that alleviate or aggravate pain and swelling.
- Nature of swelling.
  - Changes in size during a single day *or*
  - Is constant *or*
  - Increases or decreases with time
- Recent trauma, sexual activity, use of medications, presence of rashes, and weight loss.

Specific Conditions

- Acute scrotal swelling with pain
  - Torsion of the testicle
    - Acute onset of constant, severe scrotal pain aggravated by physical activity and sometimes alleviated by being still.
    - If periods of acute respite from pain occur, intermittent torsion and detorsion should be considered.
    - Nausea and vomiting may occur.
    - Possible history of incidental antecedent scrotal trauma, but pain usually occurs during rest or sleep.
  - Neonatal testicular torsion
    - Can exhibit at delivery as a nontender hard scrotal mass.
    - Occurrence after delivery is uncommon.
  - Torsion of the appendix testis
    - Onset of pain and swelling is commonly acute but can be progressive, usually occurring during rest.
    - Pain can be severe, but nausea and vomiting are less common than with testicular torsion.
  - Acute epididymitis-orchitis
    - History can reveal acute or more protracted onset of pain.
    - The patient may have fever or dysuria.
    - Epididymal inflammation may arise after scrotal trauma.
    - In the adolescent patient, a history of sexual activity or urethral discharge helps guide antibiotic treatment.
  - Henoch-Schönlein purpura
    - Onset may be insidious or acute, producing a variable degree of erythema and edema.
    - In more severe cases, the process may involve the testis and epididymis, mimicking testicular torsion.
  - Focal fat necrosis
    - Can result in scrotal pain and swelling, usually after trauma in an obese boy
  - Trauma
    - History (eg, injury from zipper entrapment of scrotal skin) can be definitive.

- Mumps orchitis
  - Rarely occurs in isolation; pain and swelling usually occur within a week after parotitis.
- Scrotal skin disease
  - History may be of limited utility.

- Scrotal swelling without pain
  - Inguinal hernias and hydroceles
    - Hernia
      - Swelling expands with increases in intra-abdominal pressure (eg, crying, bowel movements, coughing).
      - The parent or child often reports the swelling to be smallest in the morning and greatest later in the day.
    - Hydrocele
      - Whether the hydrocele is acute or whether the scrotum has been chronically enlarged is often unclear.
      - The patient may have a history of trauma to the scrotum that stimulates production of serous fluid.
      - When the scrotum changes size during the day, suspect a communicating hydrocele.
  - Tumors
    - Usually present as a hard, painless mass (or vague heavy feeling) in the testicle detected by the child, parent, or examining physician.
    - Leydig cell tumor is associated with precocious puberty.
    - Gonadoblastoma occurs in dysgenetic gonads of children with disorders of sexual differentiation carrying a Y chromosome.
  - Varicoceles
    - Dilated veins are usually asymptomatic and are detected by the patient or the physician during routine physical examination.
    - Some patients report heaviness or a dragging feeling in the scrotum.
  - Spermatoceles and epididymal cysts
    - Painless and round, they usually remain stable in size but can sometimes enlarge.

PHYSICAL EXAMINATION

- Palpate the abdomen and groin to determine whether an intra-abdominal process extends into the scrotum.
- Inspect the scrotum to look for laterality of the process and scrotal erythema.
- Palpate the scrotum to determine
  - Presence and symmetry of cremasteric reflexes
  - Testicular position
  - Presence of tenderness
  - Localization of the swelling to the intrascrotal contents
  - Presence of proximal extension into the cord
- Acute scrotal swelling with pain.
  - Torsion of the testicle
    - Scrotal erythema.
    - Swelling of the involved hemiscrotum.
    - Higher than typical position of the testis within the scrotum.
    - Inspection of the scrotum may show a horizontal rather than typical vertical orientation of the testicle.
    - Evaluation of the cremasteric reflex should begin on the contralateral side; palpate the apparently unaffected testis to confirm normal size and position.
      - Unilateral loss of the cremasteric reflex on the side of the swelling and pain highly correlates with the presence of torsion.
    - The testis should then be palpated.
      - Despite the pain this maneuver may cause, it helps differentiate torsion from epididymitis.
      - With torsion, exquisite pain is elicited on palpation from the testis, as well as from the epididymis and distal spermatic cord.
      - Actual point of torsion of the spermatic cord can sometimes be palpated.
    - Associated hydrocele may be palpated and confirmed by transillumination.
    - Tense or large hydrocele often makes examination difficult.
  - Torsion of the appendix testis
    - May demonstrate hemiscrotal erythema and swelling.
    - The blue-dot sign, with the necrotic appendage visible through the scrotal skin, can help make the diagnosis.
    - A normal cremasteric reflex is present bilaterally, and the testis is normally positioned within the scrotum.
    - Testicular discomfort, if present, is typically mild, but point tenderness may be elicited from uppermost pole of the testis near the head of the epididymis—the location of the appendages.
    - On palpation, examiner may feel a 3- to 5-mm tender indurated mass on the upper pole.

- Acute epididymitis-orchitis
  - Scrotal erythema and swelling are present, along with an intact cremasteric reflex.
  - Palpation during early phase of the inflammatory process demonstrates tenderness limited to the epididymis.
  - In the later phase, tenderness and inflammation include epididymis and testis, and the distinction between the 2 structures may be difficult to appreciate.
  - The Prehn sign (relief of pain with testicular elevation) may be positive.
- Focal fat necrosis
  - Examination shows pain and swelling limited to the scrotum and not the testis.
  - Examination can be limited by discomfort and degree of obesity.
- Trauma
  - Examination must include hemiscrotums and surrounding structures (penis, perineum), assessing for swelling, ecchymosis, and bleeding.
  - Palpation may be limited by the degree of swelling or blood in the scrotum.
  - Tenderness may be limited to testis or epididymis, depending on extent of trauma.
- Mumps orchitis
  - Tender testis
- Scrotal skin disease
  - Redness and edema limited to scrotum, with typical testicle and spermatic cord

■ Scrotal swelling without pain.

- Inguinal hernias and hydroceles
  - Feel for the testis first and keep it in mind during the rest of the examination.
  - Avoid confusing testis with contents of an incarcerated hernia.
  - Hernia.
    - A bulge in the inguinal region with fluid that can be gently reduced back into the abdomen is diagnostic of an inguinal hernia.
    - In the cooperative child who can increase his intra-abdominal pressure, this procedure may be repeatedly shown, particularly with the child standing.
    - Presence of thickened spermatic cord or silk-stocking sign (the feel of the layers of the processus vaginalis being rubbed against each other) suggests patency of the processus vaginalis or a hernia.
  - Hydrocele.
    - When fluid is limited to the testis and spermatic cord can be palpated above the fluid, a hydrocele is present.
    - Hydrocele of the spermatic cord feels distinct from the testis and is round or ovoid, possibly mimicking the presence of an additional testis.
    - Hydroceles (communicating, scrotal, or of the cord) are rarely associated with tenderness on palpation.
- Tumors
  - On palpation, mass is harder than the substance of the testis, but this distinction may be difficult to discern.
  - Mass may bulge from surface of the testis.
- Varicoceles
  - Perform physical examination with the patient in the supine and standing positions.
  - Varicocele is usually decompressed in the supine position and present in the standing position.
  - Inspection may reveal dilated veins (grade 3 of 3).
  - Increased blood pooling in veins can sometimes be prompted by a Valsalva maneuver (grade 2 of 3).
- Spermatoceles and epididymal cysts
  - Separate from the testis and can be transilluminated

DIFFERENTIAL DIAGNOSIS

Acute Scrotal Swelling With Pain

- Torsion of spermatic cord
- Torsion of appendix testis
- Acute epididymitis-orchitis
- Mumps orchitis
- Henoch-Schönlein purpura
- Trauma
- Insect bite
- Thrombosis of spermatic vein
- Fat necrosis
- Hernia
- Folliculitis
- Dermatitis, acute

Scrotal Swelling Without Pain

- Hydrocele
- Hernia
- Tumor
- Idiopathic scrotal edema
- Henoch-Schönlein purpura

Chronic Scrotal Swelling

- Hydrocele
- Hernia
- Varicocele
- Spermatocele
- Sebaceous cyst
- Tumor

LABORATORY EVALUATION

- Laboratory tests are of limited value.
- The leukocyte count may be elevated in the setting of infection.
- Urinalysis may help distinguish orchitis from torsion of the spermatic cord or testicular appendage when leukocytes or nitrites are present.
- Acute scrotal swelling with pain.
  - Torsion of the testicle
    - Urinalysis is unremarkable.
    - Although the leukocytes count may be mildly elevated, it is not discriminating.
  - Acute epididymitis-orchitis
    - Urinalysis result may prove positive for leukocytes and nitrite but is often unremarkable among adolescents.
    - The leukocyte count is usually elevated.
- Scrotal swelling without pain.
  - Inguinal hernias and hydroceles
    - Laboratory tests are useful only for incarcerated inguinal hernias, with an elevated leukocyte count and possible acidosis.
  - Tumors
    - Preoperative tumor markers (α-fetoprotein, β-human chorionic gonadotropin) should be measured and used for postoperative monitoring.
    - α-Fetoprotein is elevated with yolk sac tumors but cannot be used effectively as a tumor marker until it is no longer produced (~8 months of age).
    - Serum markers and pathologic analysis are used for staging.

IMAGING

- Ultrasonography can determine whether the scrotal swelling
  - Is fluid filled or solid
  - Arises from abdomen and extends into groin
  - Is limited to the scrotum
  - Arises from the testis or spermatic cord structures
- Ultrasonography with Doppler can assess the flow of blood into the testis, helping to differentiate torsion of the testis from an inflammatory process.
  - Benefits
    - Does not use ionizing radiation
    - Takes less time to perform than nuclear scanning
  - Drawbacks
    - Limited by user variability
    - Requires placing a probe over a sensitive area
- Nuclear scintigraphy using technetium TC 99m–pertechnetate evaluates blood flow to the testis.
  - Absence of flow results in a cold spot and suggests torsion.
  - Inflammation results in increased flow to the same area.
  - Benefits include
    - Not limited by user variability associated with ultrasonography
    - Does not require placing a probe over a tender area
  - Drawbacks include
    - Uses ionizing radiation
    - Takes longer to perform than ultrasonography, thus limiting utility when time is of the essence
  - Sensitivity and specificity of the 2 modalities are similar.
- Acute scrotal swelling with pain.
  - Torsion of the testicle
    - Imaging by Doppler ultrasonography or nuclear scintigraphy should be done if the diagnosis of testicular torsion is in question.
    - Perform imaging only when it will not delay surgical exploration if torsion exists, adding to the risk of testicular loss.
    - Absence of blood flow on Doppler ultrasonography and the presence of heterogeneous parenchyma are indicative of a "missed torsion" and a non-salvageable testis.
  - Torsion of the appendix testis
    - If an inflammatory process resulting from torsion of the appendage makes differentiation from true spermatic cord torsion impossible, imaging may be helpful.
    - Scrotal Doppler ultrasonography or nuclear scintigraphy will show normal or increased flow to ipsilateral testis.

- Acute epididymitis-orchitis
  - — Ultrasonography and nuclear scintigraphy show normal symmetric blood flow or increased blood flow to an enlarged epididymis or testis.
  - — Voiding cystourethrography has been a routine part of the evaluation, but its yield is low with a normal ultrasound and a sterile urine.
- Henoch-Schönlein purpura
  - — Concurrent Henoch-Schönlein purpura and testicular torsion has been reported; therefore, if torsion is a consideration, imaging with Doppler ultrasonography or nuclear scintigraphy is indicated to evaluate testicular blood flow.
- Trauma
  - — Scrotal ultrasonography can document the integrity of the testis and of the tunica albuginea and the adequacy of blood flow.

■ Scrotal swelling without pain.

- Inguinal hernias and hydroceles
  - — Ultrasonography can delineate scrotal contents, especially when a large or tense hydrocele limits physical examination.
  - — Ultrasonography can determine cystic or solid nature of a tense scrotal mass (eg, hydrocele, tumor) or spermatic cord mass (eg, hydrocele of the cord, paratesticular tumor).
- Tumors
  - — Scrotal ultrasonography is used to delineate the mass.
  - — Computed tomography (CT) of the retroperitoneum and chest is used for staging.
- Varicoceles
  - — Testicular size, most accurately assessed by ultrasonography, should be measured; significant loss of testicular volume is an indication for surgery.
  - — Less commonly, varicoceles may be detected only by ultrasonography (grade 1 of 3).
  - — In bilateral or right-sided varicoceles, abdominal and pelvic ultrasonography or CT is used to evaluate for possible mass occluding venous return.

TREATMENT APPROACH

■ Surgical intervention is indicated not only when testicular torsion is strongly suspected but also in equivocal cases in which torsion cannot be convincingly excluded.

SPECIFIC TREATMENT

Acute Scrotal Swelling With Pain

■ Torsion of the testicle

- Surgical intervention is indicated not only when testicular torsion is strongly suspected but also in equivocal cases when torsion cannot be convincingly excluded.
- The likelihood of salvaging the testis is highest when surgery is done shortly after onset of pain.
  - — The chance of a successful outcome dissipates rapidly with time.
- With surgery, first explore the affected testis and, when torsion is present, detorse the cord.
- Explore the contralateral testis (may have the same anatomic defect) and fix it in place to avert a future metachronous torsion.
- Reinspect the affected gonad and determine the possibility of salvage.
- If the testis can be saved, fix it in the scrotum.

■ Neonatal testicular torsion

- Salvage is rare, so emergent exploration is futile.
- At exploration, anchor contralateral testis and remove nonviable testis.

■ Torsion of appendix testis

- Management is nonsurgical.
- The patient should rest and use nonsteroidal pain relievers and cold compresses for several days to reduce inflammation, swelling, and pain.
- Surgical intervention is indicated only when acute testicular torsion cannot be excluded.
  - — In these cases, the infarcted appendage is removed at surgical exploration.

■ Acute epididymitis-orchitis

- Treat with antibiotics based on the results of the urine culture and sensitivities.
  - — In sexually active adolescents, antibiotic coverage must include gonococcal and nongonococcal sexually transmitted infections.
- Anti-inflammatory agents, scrotal elevation, and rest should be prescribed.

■ Focal fat necrosis

- Treat with rest and anti-inflammatory agents.

■ Trauma

- Testicular or spermatic cord contusions: Manage symptomatically.
- Testicular rupture requires surgical exploration, evacuation of the hematoma, debridement, and repair (when possible).
  - — A nonsurgical approach has been reported.

■ Mumps orchitis

- Treatment is symptomatic.

Scrotal Swelling Without Pain

- Inguinal hernias and hydroceles
  - Repair on diagnosis to prevent incarceration.
    - The risk of incarceration increases with time and is more likely in the young child or infant.
  - Repair communicating hydroceles on diagnosis to avert progression.
  - Perform surgery inguinally; isolate the sac from the cord structures and ligate it at the level of the internal ring.
  - Inspect the contralateral ring using diagnostic laparoscopy through the isolated ipsilateral sac.
    - If the internal ring is open, proceed with contralateral surgical correction.
  - If the hydrocele is painful, surgery should proceed sooner.
- Tumors
  - Inguinal approach is used in all cases.
  - Mature teratoma is managed by testis-sparing surgery.
    - Immature teratoma has been managed successfully without removal of testis.
  - Yolk sac tumor is managed with radical orchiectomy.
    - Platinum-based chemotherapy and retroperitoneal lymph node dissection may be needed for higher-stage disease.
  - Leydig cell tumor can be treated with tumor enucleation.
- Varicoceles
  - Indications for surgery
    - Significant loss of testicular volume
    - Abnormal semen analysis (older adolescent patients)
    - Pain
    - Very large varicoceles
  - Corrective measures (all aimed at occluding direct venous return through the internal spermatic vein to improve the likelihood of normal fertility)
    - Open surgery
    - Laparoscopic surgery
    - Radiologic ablative techniques
- Spermatoceles and epididymal cysts
  - Management typically is observation.
  - Surgery may be indicated when pain or significant enlargement is present.

WHEN TO REFER

- Acute painful scrotal swelling
- Acute hydrocele
- Hernia
- Scrotal trauma
- Cellulitis of scrotum
- Varicocele
- Testicular mass
- Paratesticular mass

WHEN TO ADMIT

- Acute painful scrotal swelling with suspected testicular torsion
- Acute hydrocele
- Scrotal trauma with suspected ruptured testicle
- Testicular mass

COMPLICATIONS

- Torsion of the testicles
  - Subsequent atrophy may still result after surgery because of vascular insult.
  - Fertility may be compromised.
- Spermatoceles and epididymal cysts
  - Postoperative scarring can obstruct the epididymal ductal system and lead to infertility.

PROGNOSIS

- Acute scrotal swelling with pain
  - Torsion of the testicle
    - Spermatogenesis may be compromised after 4–6 hours of ischemia.
    - Testicular salvage is time dependent, with universal loss of the testis after 24 hours of torsion.
  - Neonatal testicular torsion
    - Neonatal testicular torsion can exhibit at delivery as a nontender hard scrotal mass.
      - Salvage in these cases is rare.
    - Torsion may occur after delivery and then is more typical of torsion in the older patient, with greater potential for salvage if intervention is rapid.
  - Mumps orchitis
    - Infertility may occur when the condition results in atrophy of both testicles.
- Scrotal swelling without pain
  - Inguinal hernias and hydroceles
    - Most hydroceles resolve spontaneously by 1 year and should be repaired if they persist beyond this age.
  - Varicoceles
    - After corrective measures, most testes increase in size to equal that of the contralateral testis.
  - Tumor
    - Radical orchiectomy is curative in >90% of stage 1 yolk sac tumors.

DEFINITION

- Seborrheic dermatitis (SD) is a common, usually asymptomatic, dermatosis of unknown cause seen primarily in infants but also in adolescents and adults.
- Psoriasiform SD, also known as *sebopsoriasis* or *seborrhiasis,* produces features of SD and psoriasis and may represent a bridge between the 2 conditions.

SIGNS AND SYMPTOMS

- Most commonly characterized as greasy, scaly dermatitis.
- Less often characterized as psoriasiform SD.
- Rarely characterized as erythrodermic SD.
- SD in infancy is characterized by
  - Diffuse, red, crusted, and yellow scaling plaques on the vertex of the scalp
  - Similar lesions also may be found in
    - Retroauricular creases
    - Eyebrows
    - Nasolabial folds
  - Lesions appear as shiny red patches with foul-smelling scale in the folds in
    - Axillary and inguinal folds
    - Neck
    - Diaper area
- Posterior lymphadenopathy has been shown to be significantly associated with SD in patients with a negative fungal culture result.
  - Asymptomatic.
  - Distributed symmetrically.
  - Similar in adolescents.
    - Patients may note a greasy, scaling, pruritic eruption on the scalp.
    - Except for a lack of inguinal area involvement, distribution of the lesions is the same as that for infants.
  - HIV-positive children 2–5 years of age may exhibit SD with lesions similar to those seen in adolescents and adults.
    - Distinctly unusual in immunocompetent children
    - Appears to be a manifestation of HIV infection
- Psoriasiform SD.
  - Psoriasiform plaques.
    - Annular, red-brown plaques having a silvery scale
    - May be present among classic greasy, yellow, scaling lesions of SD
  - Patients may or may not have pitted nails as seen with classic psoriasis.
  - Erythrodermic SD is rare and causes widespread exfoliative erythroderma.
  - Diffuse desquamation usually begins in the flexures and then spreads.
- Patients may have signs and symptoms of systemic involvement.
  - Fever
  - Chills
  - Lymphadenopathy
  - Peripheral edema
  - Dehydration
- Involvement may be the presentation of Leiner disease.

DIFFERENTIAL DIAGNOSIS

- Atopic dermatitis
  - Usually distinguished by the presence of
    - Extreme pruritus
    - Extensoral distribution in infancy
    - Flexural distribution in older children (tending to spare the scalp and to involve hands and feet)
    - Family history in 70% of affected persons
  - SD may occur concomitantly with atopic dermatitis.
- Psoriasis
  - Common inherited papulosquamous skin disorder.
  - Characterized by well-demarcated, annular, thick, red-brown, scaling plaques usually present on
    - Trunk
    - Extensor areas on the arms
    - Knees
    - Elbows
    - Diaper area
    - Scalp
  - Characterized by nail pitting.
  - Usually lacks specific distribution and the greasy component of SD.
  - Some cases of SD may overlap with psoriasis.
  - Extensive cases of SD become persistent.
  - When the family history of psoriasis is positive, patients should be referred to a dermatologist for
    - Biopsy
    - Long-term follow-up care
- Dermatophyte infection of the scalp (tinea capitis)
  - Symptoms may include
    - Scaling
    - Pruritus
    - Redness of the scalp

- Usually results in alopecia.
- Performing a fungal culture by swabbing the affected area vigorously will yield a positive result.
- Tinea corporis appears as annular, red, scaly plaques with central clearing.
- Cultures from the skin may be obtained in a similar fashion from the scalp.
- Potassium hydroxide preparation of scales from body lesions will demonstrate septate hyphae.

- Diaper dermatitis or irritant diaper rash
  - Characterized by
    - Involvement primarily of the convex surfaces by red, scaling plaques.
    - Inguinal folds are spared.
  - In candidal diaper dermatitis, similar red, scaling plaques involve the skinfolds.
    - Satellite pustules in areas not covered by the diaper may be found.
  - SD in the diaper area involves the skinfolds.
    - No satellite lesions
- Langerhans cell histiocytoses
  - Refers to
    - Letterer-Siwe disease (diffuse disseminated histiocytosis)
    - Hand-Schüller-Christian disease
    - Eosinophilic granuloma (chronic multifocal or focal histiocytosis)
  - Letterer-Siwe disease may be confused with SD because the pattern of distribution is similar.
    - Letterer-Siwe disease is also characterized by
      - Axillary, inguinal, and oral mucosal erosions
      - Purpura
      - Petechiae
      - Hepatosplenomegaly
    - Skin biopsy will distinguish these disorders easily.
      - Recommended in cases of SD unresponsive to treatment
- Erythrodermic SD
  - Inherited immunologic disorder.
  - Characterized by
    - Generalized SD
    - Persistent diarrhea
    - Failure to thrive
    - Recurrent gram-negative infections
  - Diagnosis is made by demonstrating deficient yeast opsonic activity in the patient's serum.
  - Other immunodeficiencies and metabolic disorders may occur in an erythrodermic SD pattern.

TREATMENT APPROACH

- Effective treatment for SD may involve
  - A wide range of keratolytic agents
  - Low-potency corticosteroids
  - Antifungal therapies

SPECIFIC TREATMENTS

- The choice of medication is tailored to the age of the patient.

Infants

- A more conservative approach is suggested when treating infantile SD (cradle cap).
  - Apply mineral oil or white petrolatum to the scalp.
  - Follow with a non-medicated shampoo.
- If unresponsive, second-line agents include
  - 1%–2% salicylic acid in liquid or petrolatum form.
  - Follow with a keratolytic shampoo.
    - Sebulex
    - Neutrogena T/Sal
    - P&S
  - Salicylic acid solution or petrolatum should be applied for only 10 minutes, and then shampooed out carefully.
    - Avoid the face and, particularly, eyes because severe contact irritation may occur.
  - Follow with a topical low-potency corticosteroid.
    - 1%–2.5% hydrocortisone, Synalar solution
    - Derma-Smoothe
  - Corticosteroid solution should be applied sparingly and left on for several hours.
    - This regimen may be repeated up to twice daily as needed and then tapered.
    - Dramatic improvement occurs usually within 1 week.
- Topical antifungals, specifically the azoles, are effective.
- More recently, use of topical macrolactam immunomodulators has been successful.
- Tacrolimus has antifungal properties that contribute to its therapeutic effectiveness.
- Low-potency topical corticosteroid cream (1% hydrocortisone cream) can be used twice a day to treat lesions occurring on the
  - Face
  - Intertriginous areas
  - Diaper area
- A mid-potency corticosteroid, such as 0.1% Kenalog cream, may be used on the body twice a day.

- A mid-potency or strong halogenated corticosteroid should not be used on the
  - Face
  - Intertriginous areas
  - Diaper area
- Topical ketoconazole (Nizoral).
  - Has been used to treat adult SD
  - Has been found to be beneficial in treating infantile SD
- Lesions in the diaper and intertriginous areas may become superinfected with *Candida* species.
  - Requires topical antifungal creams twice a day in addition to a topical corticosteroid

Children and Adolescents

- Topical corticosteroids.
- Keratolytic shampoos applied to the scalp.
- Topical and oral ketoconazole may be used in severe cases.
- Psoriasiform SD of the scalp is treated as described for cradle cap.
- Psoriasiform lesions on the face and trunk respond to
  - Topical corticosteroid ointments
  - Emollients
- If lesions persist into childhood, use
  - Modified Goeckerman treatment consisting of application of a tar preparation
  - Followed by outdoor exposure to sunlight and topical corticosteroids
- Generalized erythrodermic SD may require
  - Systemic corticosteroids
  - Antibiotics to control superinfection
- Hospitalization for intravenous antibiotic administration may be required.

WHEN TO ADMIT

- Generalized erythrodermic SD may require systemic corticosteroids and antibiotics to control superinfection.
- Hospitalization for intravenous antibiotic administration may be required.

WHEN TO REFER

- Patients who do not respond to standard accepted therapy
- To rule out such conditions as psoriasis and histiocytosis

COMPLICATIONS

- Infants with SD may be
  - At increased risk of atopic dermatitis
  - At risk of psoriasis (less often)

PROGNOSIS

- Usually excellent.
- Most cases resolve within the first 6 months after birth.
- Adolescent-onset and HIV-related SD may be more persistent.
  - Usually responds readily to topical therapy

DEFINITION

- Seizures are caused by abnormal discharges of neurons.
- A seizure should be considered a symptom of systemic or central nervous system (CNS) dysfunction.
- Classification of seizures and epilepsy syndromes.
  - The terms *seizure disorder* and *epilepsy* are synonymous and applied to the condition in which a tendency for recurrent, unprovoked seizures exist.
  - Generalized seizure types include
    - Tonic-clonic (also known as *grand mal* seizures)
    - Absence
    - Myoclonic
    - Clonic
    - Tonic
    - Atonic (also known as *astatic seizures* or *drop attacks*)
  - Generalized epilepsy syndromes include
    - Lennox-Gastaut syndrome
    - Childhood absence epilepsy
    - Juvenile myoclonic epilepsy
  - Focal seizure types (formerly called *partial seizures*).
    - Without impairment of consciousness or awareness
    - With impairment of consciousness or awareness
    - Evolving to a bilateral convulsive seizure
  - Focal epilepsy syndromes.
    - Benign childhood epilepsy with centrotemporal spikes (also known as *rolandic epilepsy, sylvian seizures,* and *centrotemporal epilepsy*)
    - Epilepsia partialis continua
  - Unknown.
    - Epileptic spasms

SIGNS AND SYMPTOMS

Absence Seizures

- Generalized, nonconvulsive seizures characterized by interruption of activity, staring, and unresponsiveness.
- Usually last 5–15 seconds.
- Starts abruptly without warning and end abruptly with resumption of the child's preictal activity.
- The child may be unaware that the episode occurred.
- Unresponsiveness is sometimes accompanied by
  - Eyelid fluttering
  - Upward rotation of the eyes
  - Occasionally mild clonic movements or automatisms (eg, lip smacking, grimacing, swallowing)
- Seizures may occur >100 times per day and may interfere with the child's learning ability.
- Childhood absence epilepsy
  - Consists only of typical absence seizures with onset <8 years
  - Usually resolves before puberty

Myoclonic Seizures

- Brief, sudden muscle contractions or jerks that may involve only part of the body or may be generalized.
- May occur in clusters, especially when the child is falling asleep or shortly after awakening.
- Usually, no alteration in consciousness is associated with these seizures.

Atonic Seizures

- Sudden decrease in muscle tone that may result in head nodding or mild leg flexing.
  - More significant decreases in muscle tone may cause the child to slump to the floor.
- Usually, no alteration in consciousness is detectable.

Clonic Seizures

- The body part involved contracts and then relaxes, causing a rhythmic jerking.
- With contraction, the body part or body itself takes on the position caused by the strongest muscles that move that part, usually the antigravity muscles—arm flexors and leg and trunk extensors.
- If only one side of the body is involved, the body part will be pulled to that side or activated on that side.

Tonic Seizures

- Characterized by a sudden sustained contraction of musculature, like the beginning of a tonic-clonic seizure.
- Sometimes, when these are short, they are hard to distinguish from myoclonic events because the contraction of the muscles involved is not sustained.

Generalized Tonic-clonic Seizures

- Tonic phase
  - Sustained contraction of muscles that causes the child to fall to the ground, usually in opisthotonus.

- Extensor posturing usually occurs with tonic contraction of the diaphragm and intercostal muscles.
  - Halts respirations and, in turn, produces cyanosis
- Lasts <1 minute and is followed by the clonic phase.

- Clonic phase
  - Bilateral rhythmic jerking.
  - Jerks may be accompanied by expiratory grunts produced by diaphragmatic contractions against a closed glottis.
  - Frequency of jerks decreases as the seizure progresses, although intensity may increase.
  - The tongue may be bitten, and bowel and bladder incontinence may occur.
  - Usually stops within several minutes.
  - May be followed by vomiting, confusion, and lethargy, with gradual recovery of consciousness during minutes to hours.

Infantile Spasms

- Sudden contraction of neck, trunk, and extremity muscles.
- Spasms may be flexor, extensor, or mixed flexor-extensor.
- Spasms last only a few seconds each but often occur in clusters of ≤100 individual spasms.
- A typical episode involves dropping of the head along with abduction of the shoulders and flexion of the lower extremities.
- The infant may cry during or after the spasm.
- Pallor, flushing, grimacing, laughter, and nystagmus sometimes occur.
- Episodes are common on awakening from sleep, during drowsiness, and with feedings but are rare during sleep.
- Usually divided into symptomatic and cryptogenic groups based on the presence of a predisposing etiologic factor.
  - Symptomatic infantile spasms
    - Includes those associated with abnormal neurologic development before the onset of spasms.
    - Causes include structural abnormalities of the brain, hypoxic-ischemic insults, CNS infections or hemorrhages, and inborn errors of metabolism.
  - Cryptogenic infantile spasms
    - No etiologic factor can be found.
    - Tend to start later than the symptomatic spasms.

Lennox-Gastaut Syndrome

- Severe epileptic encephalopathy characterized by focal seizures and a variety of generalized seizures, including tonic, tonic-clonic, and atypical absence seizures, often occurring at a greater frequency than other seizure disorders.
  - Tonic seizures cause sudden, sustained contraction of the muscle groups, sometimes causing the child to fall.
  - Atypical absence seizures consist of a brief period of staring and immobility.
    - Onset and recovery of atypical absence seizures are less abrupt than those of typical absence seizures.
  - Episodes may be associated with mild tonic motor manifestations, automatisms, or loss of postural tone.
  - Atonic seizures occur and may be preceded by myoclonic jerks.
- The seizures associated with Lennox-Gastaut syndrome are often very difficult to control.

Juvenile Myoclonic Epilepsy

- Primary generalized epilepsy characterized by myoclonic jerks that affect mainly the upper extremities and, less commonly, the lower extremities.
  - Jerks usually occur shortly after awakening.
  - Patients may report clumsiness or difficulty holding objects early in the morning.
- Myoclonic jerks almost always precede the onset of generalized tonic-clonic seizures by months to years.
- In addition to myoclonic seizures
  - ~80% of patients have generalized tonic-clonic seizures.
  - 25% have absence seizures.

Focal Seizures

- Symptoms may be motor, sensory, or cognitive, depending on the location of the neuronal discharge.
  - Motor seizures
    - May be restricted to a part of the body (eg, the face, a limb) or may spread to involve the entire side.
    - May also spread to the opposite hemisphere, resulting in generalized tonic-clonic seizure activity.
    - Focal tonic-clonic seizure activity may be followed by Todd paralysis, a weakness of the limbs most involved in the seizure.

- Focal sensory seizures
  - Most often manifested by paresthesias lasting <1–2 minutes.
- May result in impaired consciousness, but, preceding impairment of consciousness, the patient may have symptoms that are referred to as the *aura*.
  - Seizure discharges from one occipital lobe may cause visual symptoms (eg, scintillating colored spots or scotoma in the visual field contralateral to the discharge).
  - Seizures with more complex visual hallucinations often progress to altered consciousness.
- Auditory seizures.
  - Manifested by hearing noises
  - Less commonly, involve elaborate, but usually nonverbal, auditory hallucinations, such as hearing music
- Seizure activity in the olfactory region.
  - Sensation of an odor, usually described as unpleasant
- Affective symptoms, such as fear or other unpleasant feelings, can occur.
- Anger and rage are extremely rare seizure manifestations but may occur during postictal confusion if the patient is restrained.
- Déjà vu, the feeling that an experience has occurred before; jamais vu, the feeling that a previously experienced sensation is unfamiliar and strange; and a rising epigastric sensation are common.
  - Young children have difficulty describing these symptoms and may say that a "funny feeling" occurred in the head or stomach.
- Staring and automatisms, which are involuntary coordinated motor activities, occur when clouding of consciousness occurs.
  - Automatisms include simple phenomena, such as chewing, lip smacking, swallowing, and hissing, as well as more complicated activities, such as picking at clothes, searching, or ambulating.
  - Automatisms are usually followed by postictal amnesia.
- The child may become tired and go to sleep.
- Focal seizures may evolve into a bilateral or generalized convulsive seizure.
  - Sometimes focal seizures generalize so quickly that they look like generalized tonic-clonic seizures from the start.

Benign Childhood Epilepsy With Centrotemporal Spikes

- Seizures typically occur during sleep.
- The child awakens with one side of the face twitching.
- Oropharyngeal muscles are also often involved, causing the child to make unintelligible gurgling sounds.
- The ipsilateral upper extremity may be involved, but the lower extremity is involved only rarely.
- In rare cases, a seizure episode will become generalized.
- Consciousness is often retained during seizure, although the child may not be able to speak.
- Most seizure episodes last <2 minutes.
- The frequency of seizures is low, with 25% of patients having a single-seizure episode and 50% having <5 episodes.

Epilepsia Partialis Continua

- Twitching is continuous and limited to one side of the body.
- Twitching frequently involves only a few muscles and occurs most often in the hand or foot.
- Consciousness is preserved, but seizure activity might weaken the extremity involved.
- Seizure activity may persist for hours to months.

Neonatal Seizures

- Subtle seizures
  - Occur in full-term and preterm neonates, usually those with severe CNS insults
  - Consist of eye deviation, blinking, sucking, swimming movements of the arms, pedaling movements of the legs, and apnea
- Clonic seizures
  - May be focal or multifocal
    - Focal clonic seizures: characterized by rhythmic jerking that remains localized and is almost always associated with electrographic seizure discharges from the central part of the opposite hemisphere
    - Multifocal clonic seizures: characterized by clonic activity in one extremity that migrates randomly, often rapidly, from side to side and place to place within the body
- Tonic seizures
  - May be focal or generalized
  - Focal tonic seizures
    - Characterized by sustained posturing of a limb or asymmetric posturing of the neck and trunk and possibly accompanying subtle seizure activity, such as eye deviation

- Generalized tonic seizures
  - Characterized by tonic extension of the limbs.
  - Less commonly, the upper extremities are flexed and the lower extremities are extended.
- In preterm neonates, they may occur at the onset of severe intraventricular bleeding.

- Myoclonic seizures
  - Flexion jerks of the upper or lower extremities.
  - Singly or in a series of repetitive jerks.
  - Sometimes associated with tonic spasms and multifocal seizures.
  - Neonates with myoclonic seizures tend to have severely abnormal dysgenetic brains or metabolic defects.
  - Occasionally cryptogenic.

Febrile Seizures

- Occur in young children with fever but no evidence of intracranial infection or acute neurologic illness.
- Simple febrile seizures are generalized tonic-clonic convulsions that last <15 minutes and do not recur within 24 hours.
- Complex febrile seizures are less common, focal or prolonged >15 minutes, and do not recur within 24 hours.

Paroxysmal Nonepileptic Events (Pseudoseizures)

- Movements are usually not clonic but may be quivering or random thrashing.
- Episodes may be dramatic, with screaming, shouting, and thrashing of the extremities.
- Usually, no incontinence, injury, or tongue biting.
- Episodes may vary greatly in the same child.
- Usually, no postictal period.

DIFFERENTIAL DIAGNOSIS

- Seizures must be differentiated from other paroxysmal disorders in childhood, such as
  - Syncope
  - Breath-holding spells
  - Staring related to inattention
  - Paroxysmal vertigo
  - Cardiac arrhythmias
  - Stereotypic behaviors
- Focal seizures with impaired consciousness
  - Differentiate from absence seizures, which are also characterized by staring and unresponsiveness.
  - Absence seizures have abrupt onset and termination; focal seizures have a more gradual onset and termination.
  - Absence seizures last <30 seconds and are not associated with postictal confusion.
  - Automatisms can occur if absence episodes are prolonged but are often just a continuation of motor activity present before onset of seizure.
- Neonatal seizures
  - Clonic seizures
    - Differentiate from benign neonatal sleep myoclonus, which consists of small-amplitude clonic activity that may wax and wane in various parts of the body.
  - Myoclonic seizures
    - Differentiate from benign myoclonic jerks that occur during sleep in neonates.
  - Febrile seizure
    - If an infant is <1 year or has not rapidly returned to normal, lumbar puncture should be strongly considered to evaluate for meningitis.
- Pseudoseizures
  - Differentiate from epileptic seizures.
    - Movements are usually not clonic but may be quivering or random thrashing.
    - Usually not associated with incontinence, injury, or tongue biting.

DIAGNOSTIC APPROACH

- Neonatal seizures
  - Electrical seizures may not have clinical correlates; hence, electroencephalogram (EEG) recording should be done for all infants at risk for seizures to identify these clinically silent electrical seizures.
- Paroxysmal nonepileptic events (PNEs) (pseudoseizures)
  - Detailed history and observation of an episode may be all that is needed to diagnose.
  - Capturing the event during video EEG monitoring establishes the diagnosis in patients in whom the distinction cannot be made clinically.
  - A prolactin level drawn within 10–20 minutes of an event may help in differentiating it from an epileptic seizure.
    - Prolactin level drawn soon after a PNE remains normal.
    - Prolactin level after a generalized tonic-clonic seizure or a focal seizure with loss of awareness is twice normal or higher.

LABORATORY FINDINGS

- Laboratory tests usually performed at the time of the initial seizure include measurement of
  - Serum electrolytes
  - Calcium
  - Magnesium
  - Blood glucose
- In some cases, history or examination may indicate that a more extensive laboratory evaluation is required.
- A complete blood cell count should be obtained before carbamazepine therapy is initiated and should be repeated after 2–3 weeks.
  - Whether further blood cell counts are useful when the initial counts are within reference ranges is unclear.
  - They should be obtained when the child is ill and are often repeated biannually or annually.
  - Neutropenia as low as 3,000/mm may occur, especially in association with a viral infection, but does not predict more serious myelosuppression.

IMAGING

- Plain radiography
  - Radiographs of the skull can detect calcifications that may be seen in some syndromes, but they rarely help in evaluating children who have epilepsy.
- Computed tomography (CT) and magnetic resonance imaging (MRI)
  - Detect structural abnormalities, such as
    - Low-grade tumors
    - Changes in myelination
    - Heterotopic gray matter
  - MRI is more sensitive than CT and, therefore, the better study when available.
  - Neuroimaging studies are not warranted in every child who has epilepsy; however, an MRI should be done in children with focal neurologic abnormalities on examination or intractable epilepsy.
- Positron emission tomography and single-photon emission CT
  - Useful in localizing metabolic alterations with seizure activity and seizure foci
  - Clinically relevant only in individuals with intractable epilepsy being evaluated for epilepsy surgery

DIAGNOSTIC PROCEDURES

- EEG
  - Measures physiologic function of the brain.
  - EEG helps define the seizure type.
    - Epileptiform EEG may support diagnosis of epilepsy, but a normal tracing does not exclude the diagnosis.
  - Other abnormalities (eg, slowing, background disorganization) are much less specific.
  - Repeat tracings increase the likelihood of detecting epileptiform discharges in patients who have seizures.
  - Procedures such as hyperventilation, photic stimulation, and sleep should be used when obtaining EEG recordings.
  - Nasopharyngeal and sphenoidal electrodes are rarely used to detect mesial temporal discharges because they rarely add to information obtained by special scalp electrode placements.
  - EEG abnormalities must be interpreted in view of the clinical symptoms.
- EEG findings, by seizure type
  - Absence seizures
    - Classic EEG finding: bilaterally synchronous 3-Hz spike-and-wave discharges.
    - Hyperventilation may be used to precipitate electrical discharge and clinical seizure.
    - Photic stimulation during EEG induces seizure discharge in some patients.
  - Generalized tonic-clonic seizures
    - Associated with bilaterally synchronous electrical discharges on EEG.
    - EEG may demonstrate focal discharge that may spread to both hemispheres or may show only bilateral synchronous discharges.
  - Infantile spasms
    - EEG pattern is known as *hypsarrhythmia*, characterized by high-voltage slow waves with irregularly interspersed multifocal spike-and-sharp waves.
    - Hypsarrhythmia may precede the onset of clinical manifestations, or it may occur later or not at all.
    - Over time, hypsarrhythmia usually evolves into other focal or generalized abnormalities; in some cases, the EEG may normalize.
  - Lennox-Gastaut syndrome
    - EEG typically shows an irregular, high-voltage, slow (≤2.5 Hz) spike-and-wave pattern.
    - Discharges are bilaterally synchronous.

- Juvenile myoclonic seizures
  - Ictal EEG typically shows generalized, symmetric polyspike and waves at 4–6 Hz.
  - Photic stimulation precipitates the electrical discharges in some patients.
- Focal seizures
  - Most common EEG finding is an anterior temporal lobe spike discharge, although some patients will have spike discharges from other areas.
  - Interictal EEG recordings may be normal.
  - Repeating the EEG increases the likelihood of demonstrating the abnormal discharge.
  - Nasopharyngeal or sphenoidal electrodes rarely add information that is not obtained by scalp recordings that include special temporal placements.
- Benign childhood epilepsy with centrotemporal spikes
  - Typical EEG findings are mid-temporal or centrotemporal spike discharges occurring unilaterally or independently bilaterally, often frequent in light sleep and sometimes induced by hyperventilation.
  - Neuroradiologic studies show no abnormalities to correlate with the EEG focus.
- Neonatal seizures
  - Subtle seizures: EEG does not always show correlation of electrical seizure discharges with the clinical seizure activity.
  - Clonic seizures: multifocal independent areas of electrical discharge.
  - Tonic seizures: often have no electrographic correlate and usually associated with severe EEG background abnormalities.
  - Myoclonic seizures: EEG usually abnormal; may show a burst suppression pattern but might not change during the myoclonic event.
- Because electrical seizures may not have clinical correlates, EEG recording should be done for all neonates and infants at risk for seizures to identify clinically silent electrical seizures.
- Febrile seizures
  - EEG usually is not helpful in evaluating children who have simple febrile seizures.
  - EEG within 1 week of the seizure often shows posterior slowing.
  - Paroxysmal activity is seen in EEGs of 35%–45% of patients who are followed for several years.
  - EEG abnormalities do not predict recurrence of febrile seizures or development of epilepsy.
  - In children with focal febrile seizures, EEG may indicate focal epileptiform abnormalities, which would be associated with an increased chance of recurrence and epilepsy.
- Pseudoseizures
  - Capturing the event during video EEG monitoring establishes the diagnosis in patients in whom the distinction cannot be made clinically.

■ Genetic studies
- In some children with unexplained epilepsy, particularly those with other neurodevelopmental or dysmorphic features, it may be important to test for specific genetic disorders.

TREATMENT APPROACH

■ Seizures in neonates
- EEG confirmation of seizure activity must be obtained to help avoid the pitfall of treating coarse jitteriness or other transient abnormal movements with antiseizure medication.
- Treatable causes must be pursued rapidly (eg, hypoglycemia, electrolyte imbalance, infection).
- Electrographic seizures may continue after clinical seizures are controlled.
  - If frequent or prolonged, further anticonvulsant therapy may be merited.
- Seizures related to acute injuries (eg, asphyxia, stroke, acute CNS infections other than herpes) are self-limited and stop after several days.
  - No evidence has been found that continuing treatment past the neonatal period will change the chance of recurrence.
  - Such seizures are usually treated short term.
  - In some nurseries, neonates are not sent home on anticonvulsants if their seizures stopped or, if they are, then anticonvulsants are continued for only a few weeks.
- Seizures related to brain malformations or inborn errors of metabolism may be much more persistent.
  - Duration of treatment depends on the neonate's clinical course.

■ Seizures in children beyond the neonatal period
- Diagnosing the seizure type correctly is the critical first step in treatment, because some seizure disorders respond to certain medications and may be exacerbated by others.

- Select the drug with the fewest adverse effects.
- Give medication at a dose that will result in a low therapeutic blood level; increase the dose until seizures are controlled or adverse effects are prominent.
- Add a second medication if the initial medication is not fully effective.
- Consider discontinuing the first medication if seizures are fully controlled with the second medication.
- Strive for monotherapy if possible; polytherapy often does not improve seizure control but may significantly increase toxicity.
- Monitor closely for potential cognitive and behavioral adverse effects of antiepileptic medications.
- To devise the optimal dosing regimen, consider pharmacokinetics of various antiepileptic medications.
- Determine dosing frequency according to half-life (time in which the serum level decreases to 50% of initial value).
  - The dosing interval should be no longer than half-life of the medication.
  - Most antiepileptic agents may be administered twice a day; some, only once daily.
  - Evaluate the efficacy of an antiepileptic medication only after 5 half-lives have elapsed because this period is required for medication to reach a steady state.
  - In antiepileptic medications that induce hepatic enzymes (eg, phenobarbital, phenytoin, carbamazepine), half-life decreases during the first weeks of treatment.
- If breakthrough seizures occur at times of low (trough) serum drug levels, toxic effects occur at times of peak drug levels, or children require higher antiepileptic medication levels, the total daily dose should be divided into more frequent doses.
- Serum drug levels can guide adjustment of doses of some antiepileptic medications.
  - Obtain a baseline level.
    - When the patient has been taking an appropriate dose long enough to have stable levels
    - To verify compliance, breakthrough seizures, and toxic effects
    - When other medications have been added or deleted from the patient's regimen
  - The timing of the sample in relation to the last dose is important for interpreting levels, especially in drugs with short half-lives.

SPECIFIC TREATMENTS

Treatment, by Type of Seizure

- Absence seizure
  - Monotherapy with ethosuximide, valproate, or lamotrigine usually controls absence seizures effectively.
    - Ethosuximide is the drug of choice if the child has only absence seizures because of its effectiveness and lower incidence of serious adverse effects.
    - Valproate and lamotrigine are the drugs of choice if the patient also has tonic-clonic seizures.
    - Any 2 of these medications may be used together when absence seizures are not completely controlled with one.
  - Benzodiazepines are effective, but adverse effects on behavior make them second-line therapeutic agents.
  - Phenytoin, phenobarbital, carbamazepine, and oxcarbazepine are usually ineffective and may exacerbate absence seizures.
- Generalized tonic-clonic seizure
  - Valproate, lamotrigine, phenobarbital, topiramate, zonisamide, and levetiracetam.
  - Focal seizures that generalize may be effectively treated with these medications, as well as with carbamazepine, oxcarbazepine, and phenytoin.
- Myoclonic seizure
  - Most drugs that help other primary generalized seizures are helpful.
  - This type of seizure may be exacerbated by the medications that are used primarily for focal seizures.
- Infantile spasm
  - Resistant to treatment with most anticonvulsants
  - Cryptogenic group
    - The treatment used most often is adrenocorticotropic hormone (ACTH).
    - ACTH in a long-acting form is administered as a single daily intramuscular dose of 20–40 IU.
    - Oral corticosteroids may be an effective and less expensive alternative.

- Adverse effects of ACTH and steroids are significant and include Cushing syndrome, hypertension, susceptibility to infections, hyperglycemia, gastrointestinal bleeding, and electrolyte disturbance.
- Symptomatic group
  - Alternative anticonvulsants may be tried before ACTH.
  - Vigabatrin is the only anticonvulsant other than ACTH with clear efficacy and is the drug of choice for infantile spasms caused by tuberous sclerosis.
  - There are reports, but not good evidence, for benzodiazepines, particularly nitrazepam, topiramate, zonisamide, and valproic acid, sometimes controlling infantile spasms.

■ Lennox-Gastaut syndrome
- Valproate is usually the initial drug of choice.
- Lamotrigine, topiramate, rufinamide, and felbamate significantly reduce frequency of atonic and generalized tonic-clonic seizures.
- Benzodiazepines, particularly clobazam, successfully control atonic, myoclonic, and atypical absence seizures.
  - With increasing doses, the frequency of adverse effects also increases.
  - Development of tolerance is a problem.
- Ethosuximide can help control atypical absence episodes.
- Phenytoin can be used for tonic seizures.
- A ketogenic diet has been beneficial in seizure control, but adherence may be a problem.

■ Juvenile myoclonic seizures
- Valproate will control myoclonic jerks, absence seizures, and generalized tonic-clonic seizures in >80% of patients but is often avoided in females of childbearing age.
- Lamotrigine, topiramate, zonisamide, and levetiracetam are effective.
- Phenytoin is not effective.
- Carbamazepine and oxcarbazepine may exacerbate seizures.

■ Focal seizures
- Anticonvulsant drugs, including carbamazepine, oxcarbazepine, and valproate.
  - These and most of the newer anticonvulsant medications are preferred over phenytoin and phenobarbital.
- Carbamazepine and oxcarbazepine are the drugs of choice in children because of their efficacy and relatively mild adverse effects.
  - If seizures are not controlled with carbamazepine, addition of acetazolamide may result in improved seizure control.
  - For some patients, oxcarbazepine is less sedating.
- Patients who have medically intractable focal seizures
  - Should be evaluated at a comprehensive epilepsy center to determine candidacy for surgery.
    - This results in complete seizure control in ≤90% of patients.

■ Benign childhood epilepsy with centrotemporal spikes
- For infrequent episodes, no treatment may be needed.
- If episodes frighten the child and treatment is initiated, carbamazepine or oxcarbazepine are the drugs of choice.
- Most anticonvulsants are effective.
- Carbamazepine and oxcarbazepine may exacerbate absence seizures in children who are prone to them.

■ Epilepsia partialis continua
- Most anticonvulsants have some efficacy, but medical control of epilepsia partialis continua is generally difficult to achieve.

■ Neonatal seizures[1]
- Ensure adequate ventilation and perfusion.
- Obtain blood for glucose, calcium, magnesium, and electrolyte studies.
- Correct any associated metabolic abnormality.
- Hypoglycemia: If glucose level is low (<40 mg/dL), immediately give 10% dextrose intravenously in a dose of 2 mL/kg.
  - Maintain blood glucose levels 40–80 mg/dL by continuous intravenous (IV) infusion.
  - Monitor the levels in full-term and preterm neonates.
  - Try to avoid significant hyperglycemia.
- Hypocalcemia: Correct by administering 5% calcium gluconate solution, 4 mL/kg, intravenously at a rate of 1 mL/min to maintain serum calcium levels >7 mg/dL while monitoring cardiac rate and rhythm.
- Hypomagnesemia: Correct serum magnesium levels to 1 mmol/L with 50% magnesium sulfate solution, 0.2 mL/kg intramuscularly.

- For continued seizure activity, consider other etiologies and administer anticonvulsants.
- Give phenobarbital in a loading dose of 20 mg/kg intravenously over 10 minutes.
  - Additional doses of 5 or 10 mg/kg can be given, up to a total of 40 mg/kg.
- Give fosphenytoin in a loading dose of 20 mg/kg of phenytoin equivalents intravenously while monitoring cardiac rhythm.
- Levetiracetam at 20–50 mg/kg has been used.
- Give lorazepam in doses of 0.1 mg/kg intravenously for persistent seizures.
  - Respiratory status should be monitored.

■ Febrile seizures
- Usually, seizure activity has stopped by the time the child is evaluated.
- If the seizure continues, administer lorazepam.
- Bring down temperature by using rectal antipyretics, removing blankets and clothing, and sponging.
- Educate the family about the benign nature of seizures, use of antipyretics, and first aid for seizures.

■ Pseudoseizures
- Treatment is directed toward the psychosocial issues involved.

Specific Antiepileptic Medications

■ **Table 1** outlines commonly used antiepileptic medications and their properties.

■ Acetazolamide.
- Effective adjunctive treatment of several types of seizures.
- Antiepileptic properties are not well understood.
- Can be used in combination with valproic acid for treatment of absence, myoclonic, and akinetic seizures.
- Adding acetazolamide to carbamazepine may improve control of focal seizures.
- Acetazolamide metabolism is not affected significantly by other medications.

■ Carbamazepine.
- An older medication but still widely used because it has relatively few effects on cognitive function.
- May positively affect behavior.
- Complete blood cell count should be obtained before carbamazepine therapy is initiated and should be repeated after 2–3 weeks.
- The dose may need to be changed during treatment because this drug tends to induce its own metabolic breakdown.
- Phenobarbital, phenytoin, and clonazepam decrease carbamazepine serum levels.

■ Clobazam.
- Approved for add-on therapy in Lennox-Gastaut syndrome in children ≥2 years.
- It is converted by subclasses of the cytochrome P450 enzymes to an active metabolite, desmethylclobazam.
  - Desmethylclobazam has about half the efficacy but is present in about 10× the concentration.
  - Desmethylclobazam and its metabolites are excreted in urine.
- Half-life is 12 hours, but that of desmethylclobazam is 40–50 hours.
- Start at a low dose (5 mg/d in children <30 kg and 10 mg/d in bigger children) and increase at 1- to 2-week intervals because of associated sedation.
  - The maximum dose suggested for children <30 kg is 20 mg/d, whereas up to twice that may be used in bigger children.
  - Caution is particularly important when adding it to other sedating medication.
  - The dose should be modified when used with felbamate, selective serotonin reuptake inhibitors, omeprazole, and oxcarbazepine because they may tend to increase its levels and the levels of its active metabolites.
- Clobazam metabolism and that of its active metabolite are markedly slowed in individuals with deficits in the cytochrome P450 enzyme system.
- When clobazam is stopped, it requires tapering over several weeks or even months if the child has been taking it for more than a few weeks.
- It may have less associated tachyphylaxis than other benzodiazepines, and the associated sedation and increased secretions are less than with clonazepam.

■ Clonazepam.
- Not a first-line antiepileptic medication because of adverse effects.
- Causes significant behavioral changes, including hyperactivity, decreased attention span, aggressiveness, and restlessness.
- Also causes increased secretions, which may be a problem in children with reactive airways or cerebral palsy and associated compromised swallowing mechanisms.
  - May lead to swallowing dysfunction in higher levels

Table 1. Common Antiepileptic Medications

Drug	Indications	Half-life (h)	Usual Daily Dose (mg/kg)	Therapeutic Levels (mcg/mL)	Adverse Effects
Acetazolamide	Absence, myoclonic, akinetic, focal	10–12	10–20	10–14	Diuresis, paresthesias, sedation, carbon dioxide retention, rashes
Carbamazepine	Focal, focal evolving to bilateral convulsive	18–55, initially 3–23 on chronic therapy	2–5 initially, 5–25	4–12	Allergic rashes, nausea, diplopia, blurry vision, dizziness, hypersensitivity, hepatitis, aplastic anemia
Clobazam	Lennox-Gastaut syndrome in children ≥2 y	12, active metabolites 40	0.1–0.2 initially, 0.6–1.0 maximum	100–300	Sedation/somnolence, increased secretions
Clonazepam	Absence, primary generalized, infantile spasms	20–36	0.01–0.05	0.01–0.07	Sedation, hyperactivity, inattention, aggressiveness, tolerance, ataxia, withdrawal seizures
Ethosuximide	Absence, myoclonic, akinetic	15–68	15–40	40–100	Nausea, abdominal discomfort, hiccups, drowsiness, behavioral problems, dystonia, myelosuppression, drug-induced lupus
Felbamate	Focal (in patients >12 years), Lennox-Gastaut syndrome	20 (in monotherapy)	15–45 (maximum 3,600 mg)	30–100	Anorexia, weight loss, nausea, insomnia, headache, fatigue, aplastic anemia
Gabapentin	Focal, focal evolving to bilateral convulsive in patients >12 years	5–7	Total daily dose 900–1,800 mg (maximum 3,600 mg)	2–20	Somnolence, dizziness, ataxia, fatigue

Table 1 (*continued*)

Drug	Indications	Half-life (h)	Usual Daily Dose (mg/kg)	Therapeutic Levels (mcg/mL)	Adverse Effects
Lacosamide	Focal in patients >17 years	13	Start 50 mg twice a day, increase 50 mg every week; top dose is 400 mg daily.	5–16	Nausea, vomiting, dizziness, increased PR interval
Lamotrigine	Focal, primary generalized, absence, atypical absence, atonic, myoclonic	7–45	Initially 0.15 if on valproate, 0.6 if on an enzyme-inducing drug, and 0.3 if on both or neither of valproate and an enzyme-inducing drug. Double the dose in 2 wk and continue slow titration over 2–3 mo to target dose.	2–14	Rash, including Stevens-Johnson syndrome, vomiting
Levetiracetam	Focal, focal evolving to bilateral convulsive, myoclonic, primary generalized tonic-clonic	6–8	Start at 10–20 mg/kg/d, increase every 2 wk; top dose 60 mg/kg or 3,000 mg	6–35	Somnolence, irritability, hostility
Oxcarbazepine	Focal, focal evolving to bilateral convulsive	4–9	10–50: start at 10 mg/kg; top dose 2,400 mg divided into 2 daily doses	15–35	Somnolence, nausea, dizziness, rash, hyponatremia
Phenobarbital	Neonatal, febrile, focal, focal evolving to bilateral convulsive, primary generalized, akinetic	36–120	3–5 (<25 kg), 2–3 (25–50 kg), 1–2 (>50 kg)	10–40	Sedation, inattention, hyperactivity, irritability, cognitive impairment, rare hypersensitivity reactions
Phenytoin	Focal, focal evolving to bilateral convulsive, generalized tonic-clonic	7–42 (nonlinear kinetics)	5–7	10–20 (or lower)	Rashes, hirsutism, gingival hyperplasia, coarse features, psychomotor slowing, neuropathy, folate deficiency, myelosuppression, drug-induced lupus

Table 1 (*continued*)

Drug	Indications	Half-life (h)	Usual Daily Dose (mg/kg)	Therapeutic Levels (mcg/mL)	Adverse Effects
Rufinamide	Lennox-Gastaut syndrome	6–10	Start 10 mg/kg divided into 2 daily doses, increase by 10 mg/kg every other day; top dose 45 mg/kg or 3,200 mg	15–30	Somnolence, fatigue, dizziness, headache, nausea, shortened QT interval
Tiagabine	Focal	3–9	Start at 0.1 up to 0.25–1.5 (maximum 30 mg)	40–100	Dizziness, somnolence, headache, depression
Topiramate	Focal, primary generalized, tonic, atonic, atypical absence, infantile spasms	20–30	1–9	2–20	Somnolence, anorexia, fatigue, difficulty with concentration, nervousness, kidney stones, oligohidrosis
Valproic acid	Primary generalized, absence, myoclonic, akinetic, febrile, infantile spasms, Lennox-Gastaut syndrome, focal	6–16	10–30, monotherapy, may need more in polytherapy	50–100 (150 if tolerated)	Nausea, tremor, weight gain, hair loss, thrombocytopenia, hepatic failure, pancreatitis
Vigabatrin	Infantile spasms	5.7 in infants to 7.5 in adults	Start 50 mg/kg divided into 2 daily doses, increase by 50 mg/kg per wk; top dose of 150–200 mg/kg	0.8–36	Visual field loss, irritability
Zonisamide	Focal, primary generalized, infantile spasms	24–60	Start at 1–2 mg/kg and may work up to 10 mg/kg; top adult dose is 600 mg.	10–40	Somnolence, dizziness, kidney stones, oligohidrosis

- Because withdrawal may cause irritability, myoclonus, and increased seizures, it should be withdrawn slowly.
- Usually reserved for myoclonic seizures that are refractory to other medications.

- Other benzodiazepines.
  - Clorazepate.
    - Least sedating of the benzodiazepines
    - Sometimes used adjunctively for resistant seizures
  - Diazepam and lorazepam may be used.
  - All benzodiazepines are associated with tachyphylaxis and some sedation and withdrawal seizures.
    - Rotating from one to another may help retain efficacy.
  - Their most significant role in epilepsy is in intermittent use, as in status epilepticus, for which IV lorazepam is the drug of choice.
  - Rectal preparation of diazepam may be administered safely during prolonged seizure outside a hospital setting.
  - These drugs may also be used
    - To stop flurries of seizures in patients predisposed to them
    - Sometimes for nocturnal seizures
- Ethosuximide.
  - Limited spectrum of efficacy.
  - Mainly for treating absence seizures and some forms of myoclonic seizures.
  - Because pancytopenia has been associated with long-term administration, periodic blood cell counts may be necessary.
  - Does not interact significantly with other antiepileptic medications.
- Felbamate.
  - 1 year after felbamate was approved and widely used because of its lack of associated sedation, >20 cases of aplastic anemia among persons taking it were reported.
    - No cases have been reported in children <13 years.
    - Should be used only in children whose epilepsy does not respond to other drugs appropriate to the seizure type and in whom the potential benefits of treatment outweigh the low risk of aplastic anemia.
  - Interacts with phenytoin, carbamazepine, and valproate; therefore, doses of these medications must be reduced by 25%–50% when felbamate is added.
  - Felbamate levels are lowered by medications that induce liver enzymes; consequently, felbamate doses may need to be increased.
- Gabapentin.
  - Approved as adjunctive therapy for focal seizures and focal seizures evolving to bilateral convulsive seizures in children ≥3 years.
  - Significantly reduces seizure frequency in children refractory to conventional anticonvulsants but has not proved as effective an anticonvulsant as most other agents.
  - Currently used more for neuropathic pain than for seizure control.
  - Does not interact with other drugs and is 100% excreted renally, offering an advantage to children with liver failure.
- Lacosamide.
  - Approved as adjunctive therapy for focal seizures in patients ≥17 years
  - No significant interactions with other antiepileptic drugs but may potentiate generalized seizures
- Lamotrigine.
  - Approved for treating focal seizures in individuals >16 years and as add-on therapy in children ≥2 years with Lennox-Gastaut syndrome.
  - Reduces frequency of focal and generalized seizures.
  - Has no effect on metabolism of other antiepileptic drugs; however, phenobarbital, phenytoin, and carbamazepine decrease the half-life of lamotrigine.
  - Valproic acid increases the half-life of lamotrigine by 2- or 3-fold; therefore, doses of lamotrigine should be lower when given with valproic acid.
  - The range of therapeutic plasma concentrations is wide (1–≥14 mcg/mL), making monitoring of serum levels less useful.
  - Side effects may not be seen with levels as high as 16–18 mcg/mL.
  - Recommended starting doses are
    - 0.15 mg/kg when used in combination with valproate, 0.6 mg/kg when used with an enzyme-inducing drug but *not* valproate, and 0.3 mg/kg when used with both or neither of valproate and an enzyme-inducing drug.
    - Starting dose is doubled after 2 weeks and tripled after another 2 weeks; then doses may be increased in larger increments, taking 2–3 months to get to the target dose.

- Levetiracetam.
  - Approved as adjunctive therapy for focal seizures in children ≥4 years, for myoclonic seizures in patients ≥12 years, and for primary generalized tonic-clonic seizures in patients ≥6 years.
  - The lack of significant adverse effects and drug interactions has made levetiracetam an initial choice, especially for primary generalized seizures.
  - The irritability that may be associated with this drug can be improved by taking 50–100 mg a day of pyridoxine.
- Oxcarbazepine.
  - Approved for initial monotherapy and adjunctive therapy for focal seizures in children ≥2 years
  - Rapidly becoming a drug of first choice for focal seizures
  - Well tolerated in infants and young children
- Phenobarbital.
  - With its long half-life, it requires dosing only once or twice a day.
  - Relatively safe in terms of serious toxic effects, so monitoring parameters other than serum levels is not necessary.
  - Major disadvantage: effect on behavior and cognitive function.
    - Maintaining serum levels at the minimum for seizure control may help decrease adverse effects.
  - Phenobarbital administration will decrease serum levels of carbamazepine and valproate.
  - Administration of valproate will increase phenobarbital levels.
    - Phenobarbital doses should be decreased by 25%–50% to prevent toxic effects when prescribed concomitantly with valproate.
  - The dose per kilogram decreases as body weight increases.
    - Failure to decrease the per-kilogram dose levels in older children will result in toxic levels.
- Phenytoin (fosphenytoin).
  - Used infrequently for long-term therapy because alternatives with fewer adverse effects and more steady pharmacokinetics are available.
  - Changes in dose should be monitored via serum levels; only small dose changes should be made when levels are close to or within therapeutic range.
  - Valproic acid may decrease the total serum phenytoin levels, but the free phenytoin level transiently increases and then returns to its original level; thus, no adjustment in dose is necessary.
  - Phenytoin may decrease carbamazepine levels and increase phenobarbital levels.
  - Commonly used for treatment of status epilepticus because IV administration results in rapid penetration into the CNS.
  - Effective antiepileptic agent in generalized tonic-clonic and focal seizures; however, adverse effects limit its use.
  - Fosphenytoin is a water-soluble prodrug of phenytoin.
    - More neutral pH
    - Less tissue irritation
    - Can be administered intravenously or intramuscularly, whereas phenytoin may not be used intramuscularly
- Rufinamide.
  - Approved as adjunctive therapy of Lennox-Gastaut syndrome in children ≥4 years.
  - Contraindicated in children who have familial short QT interval.
  - Minimal effects on other antiepileptic drug levels but can lower carbamazepine and lamotrigine levels and increase phenobarbital and phenytoin levels.
  - Phenytoin, phenobarbital, and carbamazepine all decrease plasma concentration of rufinamide, and valproate increases it.
- Tiagabine.
  - Approved as adjunctive therapy of focal seizures in adults and children ≥12 years.
  - Its efficacy in generalized seizures is unclear.
  - Enzyme inducers (eg, carbamazepine, phenytoin, phenobarbital) lower tiagabine levels.
  - Used only infrequently for seizure control in children because other anticonvulsants are more effective.
- Topiramate.
  - Approved for
    - Initial monotherapy for focal seizures and primary generalized tonic-clonic seizures in patients ≥10 years
    - Adjunctive therapy in children ≥2 years for focal and primary generalized tonic-clonic seizures and for Lennox-Gastaut syndrome

- Minimal effect on metabolism of other antiepileptic drugs
  - However, concomitant therapy with phenytoin or carbamazepine will decrease topiramate levels.
- Has been effective for treating infantile spasms in some children
- Now also used for mood disorders and headache prevention

- Valproic acid.
  - Broad spectrum of efficacy and only minimal cognitive adverse effects.
  - Rarely, has been associated with fatal hepatotoxicity.
    - Most cases occur during the first 3 months of treatment.
    - Greatest risk for hepatotoxicity are children <2 years who receive valproic acid as part of antiepileptic polytherapy.
    - Valproic acid should be administered extremely cautiously to children with preexisting hepatic dysfunction.
    - Liver function should be monitored in children taking valproic acid, especially those in the high-risk group.
  - Valproic acid raises the level of phenobarbital; therefore, the phenobarbital dose must be decreased by 25%–50% if valproic acid is added.
  - Carbamazepine, phenobarbital, and phenytoin decrease valproic acid serum levels.
- Vigabatrin.
  - Approved as adjunctive therapy in adults with medically refractory focal seizures with impaired consciousness and in children 1 month–2 years of age with infantile spasms
  - May be particularly effective in infantile spasms related to tuberous sclerosis
  - Adverse effects may include
    - Irreversible peripheral visual field loss; increased risk in males, with longer length of treatment, and with higher cumulative vigabatrin dose
    - White matter vacuolation
    - Intramyelinic edema
- Zonisamide.
  - Approved as adjunctive therapy in adults with focal seizures.
  - Few studies have evaluated its use in children in the United States.
  - In Japan, where it has been available longer, zonisamide is used widely in children with focal and primary generalized epilepsy and infantile spasms.
  - Half-life of 24–60 hours allows once-a-day dosing.

Other Treatments

- Ketogenic diet
  - Effective alternative treatment for some children.
  - Half of children with intractable epilepsy showed a 50% decrease in seizure frequency; some were seizure free at 1 year.
  - To achieve ketosis, the child is given a high-fat, adequate protein, and low-carbohydrate diet, sometimes with calorie restriction.
    - The child is usually admitted to the hospital to initiate the diet, which allows monitoring for hypoglycemia and other complications, such as intolerance of the high-fat content.
    - Before and during hospitalization, a dietitian teaches the parents about the diet, giving them sample menus and explaining how to measure foods.
    - The first 24 hours of fasting to initiate the diet is no longer adhered to.
    - Strict adherence is required for success.
    - Complications of the diet include constipation, renal stones, fatigue, and metabolic acidosis.
- Vagal nerve stimulation
  - Device is surgically implanted subcutaneously in the anterior chest wall to stimulate the left vagus nerve.
  - Most studies report ~50% improvement of seizure frequency in half of children, with a few becoming seizure free.
  - Stimulation is associated with alertness, a benefit to many children with intractable epilepsy who often have been experiencing sedation from their anticonvulsant therapy.
  - Adverse effects: generally uncommon and mild.
    - Infection
    - Hoarseness
    - Neck pain
    - Insomnia
    - Occasionally, emergence of behavioral abnormalities (which may be related to increasing alertness)

- Addressing psychosocial issues
  - Parents and children may have many fears and need reassurance.
    - Explain the terms *epilepsy* and *seizure disorder.*
    - Help parents understand that diagnosis of epilepsy does not mean that their child has intellectual disability or a psychiatric disorder.
    - Give guidelines on what to do when their child has a seizure, including positioning on the side and putting nothing in the mouth.
    - Emphasize to parents that death from a seizure is rare.
  - Discuss activities of children with seizures.
    - Activities should be restricted as little as possible.
    - A child with a seizure disorder should not swim alone or go bike riding without a helmet (as for all children).
    - Contact sports are permissible when epilepsy is controlled.
    - The decision about climbing up to certain heights should be based on how well seizures are controlled.
    - Children with epilepsy should take showers rather than baths as soon as they are old enough and should not be allowed to bathe unattended.

WHEN TO ADMIT

- Seizures are acutely uncontrolled or prolonged.
- Video EEG monitoring is needed.
- Rapid changes of anticonvulsant doses are needed, resulting in a risk for marked increase in seizures.
- Ketogenic diet is initiated.

WHEN TO REFER

- Type of seizure is unclear.
- The need to treat, choice of medication, or dose of medication is unclear.
- Seizures are refractory to medication.
- Infantile spasms are suspected—a reason for an urgent consult.

FOLLOW-UP

- Discontinuation of antiepileptic therapy
  - After seizures have been controlled for 2 years, discontinuing antiepileptic medications should be considered.
  - Studies have shown that ~75% of children seizure free for >2 years remained seizure free after medications were discontinued.
  - In children with idiopathic epilepsy and typical EEG, the prognosis for remaining seizure free after discontinuation of medications is good, except in juvenile myoclonic epilepsy.
    - If EEG shows slowing, risk of seizure recurrence is higher.
  - Risk of recurrence is not increased if medication is tapered over ≥6 weeks.
  - 50% of recurrences occur within 6 months and 60%–80% within 2 years.
- Intractable seizures
  - When seizures continue despite anticonvulsants, 3 possibilities should be considered before deciding that seizures are intractable to therapy.
    - Seizures may be occurring when the child has lower blood levels of medication because of incomplete adherence or because dosing intervals are too long.
    - Medication may not be appropriate to the seizure type.
      - Primary generalized seizures will often not respond and may even worsen if treated with medications indicated for focal seizures (eg, carbamazepine, phenytoin).
    - Repeated events may represent a non-epileptiform paroxysmal disorder rather than electrical seizure.
      - Pseudoseizures can be especially difficult to differentiate from seizures because they tend to occur in persons with epilepsy.
  - If the child is having electrographic seizures that continue despite appropriate amounts of correct medications, the child has intractable seizures.

COMPLICATIONS

- Learning and behavioral problems.
  - Children with epilepsy and without global cognitive disability tend to have more learning problems, especially reading problems and attention deficit, than children without epilepsy.
  - Behavioral problems may be identified in ≤50% of children with epilepsy, and this number may increase with added adverse effects of medication and burden of a chronic disorder.
- The risk of subsequent epilepsy in children with febrile seizures is <5%.
- Factors associated with subsequent afebrile focal seizures include
  - Focal febrile seizures
  - Prolonged seizures

- Repeated episodes of seizures with the same febrile illness

- Factors associated with development of afebrile, generalized seizures include
  - >3 febrile seizures
  - Family history of afebrile seizures
  - >3 years at the time of the first febrile seizure

PROGNOSIS

- Risk of seizure recurrence is important when deciding whether to initiate antiepileptic therapy.
- Some types of seizures (eg, absence, myoclonic, and akinetic seizures; infantile spasms) have a recurrence rate of almost 100%.
  - Seizures have usually recurred by the time the child is seen by a primary care physician.
  - These seizures require treatment.
  - Children with generalized tonic-clonic or focal seizures have a recurrence risk of ~40%.
  - Factors that increase risk of recurrence include
    - Focal seizure with impaired consciousness
    - Abnormal neurologic examination
    - Focal epileptiform abnormalities on EEG
- The best prognosis is in children with a generalized seizure, normal neurologic examination, and a non-epileptiform EEG.
- >50% of recurrences occur within 6 months, ≤69% within 1 year, and 88% within 2 years.
- For intractable seizures, if epilepsy surgery is performed soon after intractability has been established
  - Some of the secondary physiologic and psychosocial effects of growing up with epilepsy may be prevented *and*
  - Children are more likely to be able to live up to their potential in adult life.
- Infantile spasms
  - Prognosis remains grave.
  - Average mortality is ~20%.
    - Aspiration pneumonia related to severe developmental abnormalities is a common cause of death.
  - ~80% of survivors are intellectually disabled.
  - Spasms usually remit by a few years of age, but 55%–60% of children subsequently develop other forms of seizures.
  - Prognosis is more favorable for infants whose neurologic development was normal before onset of spasms.
- Lennox-Gastaut syndrome
  - Otherwise healthy preschool-aged children with normal background and fast polyspike-and-wave changes on EEG have a much better prognosis for seizure control and cognitive development.
- Juvenile myoclonic seizures
  - The rate of seizure recurrence among children who discontinue therapy during early adulthood is high.
  - A 25-year follow-up study found that ≤30% may be seizure free or have only morning myoclonic seizures on no medication.
- Benign childhood epilepsy with centrotemporal spikes
  - Remits when child is ~9–12 years of age (no later than 17 years of age).
  - Remission is long lasting.
  - No associated developmental or neurologic impairment, other than some increased incidence of attention deficit or possibly some minor learning difficulties.
- Neonatal seizures
  - The prognosis of neonatal seizures relates to the underlying diseases that caused them.
  - Intellectual disability and cerebral palsy are more common sequelae than seizures.
  - Neonates who have seizures related to hypoxic-ischemic encephalopathy, hypoglycemia, or bacterial meningitis have a 50% chance of typical development.
  - Neonates whose seizures result from late-onset hypocalcemia and primary subarachnoid hemorrhage have a >90% chance of typical development.
  - The interictal EEG is helpful in determining the prognosis.
    - A normal background EEG pattern is usually associated with a good neurologic outcome.
    - A markedly abnormal background pattern, such as burst suppression or marked suppression of voltage, is associated with a high risk for neurologic sequelae.
  - Clonic type: self-limited and not associated with later epilepsy.
  - Myoclonic type: Neonates with these seizures may later develop infantile spasms.
- Febrile seizure
  - One-third of children who have a febrile seizure will have another one with another febrile illness.

- The younger the child is at the time of the first episode, the greater the risk of recurrence.
- ~50% of recurrences occur within 6 months of the initial seizure; 75% occur within 1 year.

■ Prognosis for remission
- Good for children with a younger age of onset and in whom absence is the sole seizure type
- Less favorable for those who have associated tonic-clonic seizures

PREVENTION

■ Febrile seizures
- Oral diazepam (0.33 mg/kg of body weight administered every 8 hours during febrile illness) reduces the risk of recurrent febrile seizures.
- Administering phenobarbital at onset of a febrile illness does not prevent seizure activity because therapeutic blood levels are not achieved soon enough.
- Prophylactic treatment with anticonvulsant agents may be considered if
  — Neurologic development is abnormal.
  — Seizure is complex febrile.
- Administering phenobarbital in doses that achieve blood levels of 15 mcg/mL reduces recurrence of febrile seizures.
- Valproate appears to be effective in prophylaxis.
- Phenytoin and carbamazepine do not prevent recurrences.
- Adverse effects of anticonvulsant therapy must be weighed against possible benefits.

REFERENCE

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Self-harm

DEFINITION

- Self-harm falls into 2 categories.
  - Self-injury with intent to die (suicidal behaviors)
  - Self-injury without intent to die (non-suicidal self-injurious behaviors [SIBs])
    - Non-suicidal self-injury (NSSI)
    - SIB, most common among children
- NSSI is deliberate destruction of one's own body tissue without suicidal intent and for purposes not socially sanctioned.
  - Also called self-mutilation, self-harm, and parasuicide
  - Excludes
    - Piercings and tattoos
    - Extreme forms of body mutilation (eg, amputation, enucleation) seen in patients with psychosis
    - Stereotypical self-injury seen among individuals with intellectual and developmental disabilities (IDDs)
  - Includes superficial to moderate
    - Self-cutting
    - Burning
    - Scratching
    - Bruising
  - Occurs among typically developing children and adolescents
  - Often engaged in repetitively over long periods, with increasing severity
  - Significant risk factor for future suicidal behaviors
  - Can result in medical complications, infection, or permanent scarring
- SIB refers to physical acts directed to one's own body that result in tissue damage or that can produce tissue damage if left unchecked.
  - Most common forms of SIB are
    - Head banging
    - Biting
    - Scratching
    - Pinching
    - Rubbing
  - Among the most disturbing and serious of all behaviors exhibited by children with IDDs because of implications for health and quality of life.
  - Often leads to increased risk for institutionalization and social stigmatization and decreased opportunities to learn.

HISTORY

- NSSI
  - Largely a hidden behavior.
    - Most engaging in the behavior make great efforts to keep it secret, perhaps revealing only to friends or peers in online communities.
  - Often overlooked in males or when methods of injury other than self-cutting are involved.
  - Physicians often misidentify NSSI as a suicide attempt, physical abuse, or underlying disorder (eg, borderline personality disorder [BPD], eating disorders).
  - Effective treatment begins with appropriate assessment.
    - Full history of the behavior, including age of onset.
    - Incidence over time and specific aspects of the behavior over time.
    - History of method(s).
    - Frequency.
    - Location(s).
    - Number of injuries per episode.
    - Medical severity of injuries.
    - Variables may change with time, increasing in severity or waxing and waning to reflect periods of stress.
  - Assessment includes evaluation of risk for suicide, physical injury, and the presence of other co-occurring risk factors.
    - There is no simple formula for determining whether a youth is at high or low risk.
    - Risk level status increases with
      - Increased risk for suicide or physical injury
      - Significant mental health concerns
    - Many patients who self-injure remain in the low-risk category.
      - These patients may have mild, nonclinical levels of depression, anxiety, negative body image, or self-derogation.
      - They may seem to be functioning extremely well academically, socially, and within their home environment.
- SIB
  - Can have pattern-mark appearances and can be mistaken for physical abuse.
  - Children with developmental disabilities may be at higher risk for abuse or neglect.

- Often includes
  - Biting hands, arms, or lips
  - Banging head on solid surfaces
  - Hitting head or face with a closed fist or open palm
  - Eye poking
  - Scratching, picking, pinching, or rubbing skin

PHYSICAL EXAMINATION

- NSSI
  - Physical examination shows fresh injuries, scars, burns, or unexplained bruises.
  - Some individuals limit themselves to pin or razor blade scratching that they may explain as "cat scratches."
  - Physicians aware of NSSI are cautious about interpreting signs of injury (eg, bruising, burning, cutting) as signs of physical abuse (by another).
- SIB
  - Evaluate a child with IDDs presenting with SIB for
    - Any possible illness
    - Acute or chronic condition that may be painful
  - Behavioral evaluation of SIB is predicated on 3 assumptions.
    - SIB is functional, learned behavior (ie, a function of circumstances and consequences).
    - Momentary likelihood of SIB is influenced by antecedent stimulus conditions.
      - Occurs more often in the presence of certain people, places, materials, demand contexts, and biological states than in others
    - Intervention linked to function (ie, related to antecedents and consequences) rather than form.

DIFFERENTIAL DIAGNOSIS

- NSSI.
  - Important to distinguish between NSSI and suicidal behaviors
- Suicide attempts: behaviors that may or may not result in injury, for which there is intent to die.
- NSSI: behavior in which immediate tissue damage is present but for which there is no intent to die.
- Suicidal behaviors express a wish to stop living; NSSI is reported by the youth as an attempt to feel better.
- Suicidal behaviors and NSSI are not mutually exclusive.
- NSSI may be similar to and co-occur with those of other mental health issues; know how to effectively assess and monitor
  - Mood disorder
  - Anxiety disorder
  - Impulse control/conduct problems
  - Uncontrolled anger
  - BPD
  - Alcohol or substance abuse
  - Eating disorders
- SIB.
  - IDD-related syndromes tending to occur with SIB include
    - Lesch-Nyhan syndrome
    - Fragile X syndrome
    - de Lange syndrome
    - Prader-Willi syndrome
    - Rett syndrome
  - Unclear whether there are mechanisms specific to any single genetic disorder and the expression of SIB, but it is unlikely.

SPECIFIC TREATMENT

NSSI

- Research has found that engaging in NSSI (even if only a few times) indicates problematic emotional regulation and need for intervention to develop adaptive coping strategies.
- Risk level for suicide is substantial and subject to change over time, so regular reassessment is essential.
- Dialectal behavior therapy (DBT).
  - Only treatment approach with some empirical support.
  - In studies, this approach is effective with individuals with severe NSSI and co-occurring suicidal behaviors.
  - Focuses on specific treatment goals in a hierarchy of importance.
    - Decreasing life-threatening and NSSI behaviors
    - Eliminating behaviors that interfere with therapy
    - Decreasing behaviors that interfere with quality of life (eg, substance abuse, high-risk sex)
    - Skills training in mindfulness, distress tolerance, emotion regulation, and interpersonal effectiveness to help manage psychological distress

- This approach is intensive and requires a therapist trained in DBT.
- Less intensive approaches that incorporate mindfulness, distress tolerance, emotion regulation, and interpersonal skills may be effective.

SIB

- Treating the underlying medical condition may reduce SIB.
- The evidence for SIB treatment based on behavioral evaluation is large and growing.
- Best practice calls for linking behavioral evaluation results directly to intervention strategies that include
  - Modifications to the antecedent environment to limit variables known to be associated with the onset of self-injury
  - Decreasing self-injury by emphasizing reinforcement of desired behavior and de-emphasizing punishment
- Individualize specifics of any treatment regimen with respect to
  - Patient preferences, strengths, needs, and scope of SIB
  - Caregivers' preferences, strengths, capacities, and available family and community supports
- SIB can be reduced to different degrees by agents that have actions in neurochemical systems shown to be associated with SIB.
  - It is not clear who will respond to what medication under what circumstances.

WHEN TO REFER

NSSI

- Following initial risk assessment
- Emotional regulation difficulties or poor coping strategies

SIB

- After eliminating possibility of underlying medical conditions, refer the patient to a board-certified behavior analyst.
  - Two broad categories of clinical evaluation procedures are available: functional assessment and functional analysis.
  - Both generate information about environmental antecedents to consequences of behavior that can be directly linked to interventions.
- Functional assessment.
  - Describes contextual and antecedent precursors to behavior and outcomes of behavior.
  - Typically administered face-to-face.
  - Can be completed in ~1 hour (depending on the behavioral complexity level of information desired).
  - Time-efficient survey forms for caregivers at home or school.
    - The Questions About Behavioral Function
    - Functional Analysis Screening Tool
    - Motivation Assessment Scale
  - Corroborate interview and survey information with observations of the behavior.
    - Instruments generate hypotheses about the function of SIB that are different from observational accounts.
    - Effective interventions can be developed based on the hypotheses.
- Functional analysis.
  - Systematic manipulation of the antecedents to and consequences for SIB
    - Direct observation of the effects of these consequences.
    - Children are evaluated in clinical settings.
    - Occurrence of SIB is compared across test and control conditions to determine whether SIB is sensitive to social consequences.
    - Consequences evaluated are possible positive and negative reinforcers in the form of
      - Attention from others
      - Escape from task demands
      - Access to tangible items
      - Other preferred situations
    - Causal claims between SIB and its consequences result from presentations of antecedent and consequence stimuli arranged systematically in a single-subject experimental design.
    - Requires highly trained professionals to administer and interpret.
    - Supports prompt implementation of appropriate interventions.

WHEN TO ADMIT

- NSSI
  - Threat of suicide
  - Serious physical injury
  - Underlying psychiatric conditions

FOLLOW-UP

- NSSI
  - Regular follow-up and suicide risk assessment
- SIB
  - Ongoing need for intensive intervention with an emphasis on sustainability by incumbent supports

COMPLICATIONS

- Mild, moderate, or permanent tissue damage and disfigurement, possibly life-threatening, can occur if SIB is left untreated.

PROGNOSIS

- NSSI
  - Excellent for most youth who engage at a low or moderate severity level.
  - Many individuals will stop and not resume the behavior; some will relapse and show sharp escalation in severity following a stressor.
  - As a group they remain at significantly greater risk for suicide.
- SIB
  - Despite tremendous advances, there is little evidence that the long-term burden on families and society has decreased.

DEFINITION

- Repetitive and self-stimulating behaviors include
  - Head banging and rocking
    - Rhythmic movements of the head and sometimes the entire body against a solid object
  - Thumb-sucking and nail-biting
  - Masturbation
  - Hair pulling and twisting
    - Trichotillomania (pulling out the hair)

HISTORY

- Head banging and rocking
  - Most common at bedtime or at times of fatigue or stress.
  - May vary in duration from several minutes to hours.
  - Often continues even when the child is asleep.
  - Occasionally, a family history of such behavior can be found.
    - Only 20% of siblings of children who rock exhibit similar or other rhythmic pattern disturbances.
  - Individual constitutional patterns in childhood account for wide variability in the amount of stimulation any particular child requires.
  - Marked rhythmic movements are commonly found in children with
    - Hearing or sight impairment
    - Emotional disturbance
    - Severe intellectual disability
  - Movements may represent a compensatory reaction for lack of stimuli or the inability to integrate stimuli.
  - Head banging in children with severe disabilities can be a form of functional communication; a child may increase head banging to receive parental attention or to avoid task demands.
  - A child who has no disability but who is inactive because of physical illness generally shows a need for motor release.
    - Often characterized by body rocking or other rhythmic body movements
    - Generally disappears once normal mobility is restored
  - Studies indicate no connection between rocking behavior and parental divorce or separation.
    - However, the question of inadequate stimulation should be raised.
    - The presence of family turmoil and stress should be investigated.
- Thumb-sucking and nail-biting
  - Family history appears to exist in most cases.
    - This habit is so common that an apparent association may be of no significance.
  - No apparent correlation has been found with
    - Number of children in the family
    - Birth order
    - Type of feeding or feeding schedule
    - Age or race of the parents
  - A significant association exists with the time of weaning.
    - The later weaning takes place, the less likely the chance of thumb-sucking.
    - Underlying causes of tension should also be investigated.
  - Many families substitute artificial pacifiers as a more socially acceptable means of oral pleasure.
    - Children often spontaneously suck a security blanket, doll, or stuffed animal.
  - Thumb-sucking usually occurs
    - With stress or boredom or at bedtime, when young children use it to help themselves fall asleep
- Hair pulling and twisting
  - Often indicates the presence of psychological stress

PHYSICAL EXAMINATION

- Head banging and rocking
  - Most children will be predominantly within normal limits on physical and neurologic examination.
  - Psychosocial growth and development are apparently not disturbed.
- Thumb-sucking and nail-biting
  - Increased probability of dental malocclusion if thumb-sucking continues after the eruption of permanent teeth
  - Increased incidence of digital cutaneous infections
- Hair pulling and twisting (trichotillomania)
  - The scalp is the most common area affected.
  - The eyebrows and eyelashes are the next most likely sites.
  - Trichobezoar in the stomach if the child ingests the hair.
    - Serious problem that often results in hospitalization for surgical removal of the accumulated matted hair
  - Local irritation from a dermatologic condition.
    - Rarely the cause of this disorder, but the possibility should be investigated.

DIFFERENTIAL DIAGNOSIS

- Masturbation
  - Exclude
    - Local genital irritation
    - *Candida* infection
    - Pinworm
- Infantile autism spectrum disorder (ASD) or childhood schizophrenia
  - Body twirling or spinning
  - Hand or arm flapping
- Special problems in severely intellectually disabled or emotionally disturbed children
  - Excessive rocking behavior.
  - Severe self-mutilating behaviors (Lesch-Nyhan syndrome, de Lange syndrome).
    - Compulsive self-biting
    - Severe head banging
    - Skin gouging
  - Prader-Willi syndrome.
    - Severe skin picking
  - These behaviors are part of a symptom complex in a severe disorder, in contrast with generally isolated behavior in normal children.
  - The cause is generally linked to the basic disorder and may also reflect the lack, or disordered integration, of sensory stimuli.

DIAGNOSTIC PROCEDURES

- Electroencephalography
  - Not indicated in head banging and rocking because findings are generally not helpful

TREATMENT APPROACH

- Most of these behaviors are self-limited to the preschool period and are usually viewed as normal, common, and expected behaviors.
- These habits generally do not signify psychological maladjustment.
- They often require little intervention other than reassuring parents and suggesting adequate stimulation of their child.

SPECIFIC TREATMENT

Head Banging and Rocking

- Treatment is generally directed toward assuring the parents that
  - Head banging cannot cause brain injury.
  - The child will show no adverse neurologic effects in later life.
  - Children who engage in head-banging behavior usually grow up as completely normal, coordinated children.
- Securing the crib to prevent rolling may help during the limited rocking behavior, but crib bumpers are not recommended because of concerns of suffocation, strangulation, or entrapment.
- Sedation in the form of diphenhydramine may prove effective.
- Psychotropic medication is generally unnecessary and is thus discouraged.
- Parents should not visit the child frequently at night because doing so could reinforce what may become an attention-seeking behavior.
- Rarely, if ever, do fractures of the skull or cerebral hemorrhages result from head banging in typically developing children.
  - Soft-tissue swelling and scalp contusions have been reported.
  - A protective helmet may be advised in severe cases (intracranial injuries and retinal detachment have been reported in children with ASD and severe intellectual disabilities).

Thumb-sucking and Nail-biting

- Parents.
  - Clarify with them the nature of these habits.
  - Advise parents to avoid punishment, shaming the child, threats, or anger.
  - Encouragement instead of restrictions helps engage children in their own program to decrease or eliminate the behavior.
- Simple behavioral therapy (based on positive reinforcement) is often sufficient to alleviate the habit.
  - The choice of reinforcement reward should be the child's.
- Bitter-tasting commercial preparations.
  - May be applied to the fingers as a reminder.
  - These preparations are generally inadequate unless supplemented by consistent positive reinforcement.
  - A combination of aversive taste treatment and a reward system appears to be effective in treating chronic thumb-sucking.
- Hypnosis is often successful and poses no danger.
- Psychotropic medications are of little value.

Masturbation

- Counsel parents about healthy childhood sexual development and masturbatory practices.
- Emphasize that masturbation is
  - Normal
  - Harmless

- Almost universal and a healthy practice that helps the child to derive pleasure from his or her own body
- Dispel persistent myths or beliefs that masturbation is a definitive sign of sexual abuse and that it may cause
  - Intellectual disability
  - Physical deformity
  - Blindness
  - Poor physical and mental health
  - Facial pimples
  - Hair on the palms of the hand
  - Homosexuality
  - Sexual perversions
- Encourage parents to avoid punishing or shaming their child for a normal behavior.
  - Negative parental reactions will not reduce the frequency of masturbation but can lead to feelings of guilt and shame in children.
- If parents observe masturbatory activity in their child
  - Suggest to the child the inappropriateness of manipulating their genitalia in public places or in front of others.
  - Inform the child that certain practices, such as using the toilet and masturbating, are best carried out in private.
- Counseling and advice given by the practitioner may be met with covert or overt resistance by parents or school authorities.
  - The pediatrician should be well prepared to educate persons responsible for the growth and development of children.

Hair Pulling and Twisting

- Treatment is usually indicated.
- Behavioral therapy should be used as first-line treatment.
- Research does not support the use of selective serotonin reuptake inhibitors (SSRIs) to treat trichotillomania, but SSRIs can treat comorbid anxiety.
- Although studies of the treatment of adult trichotillomania showed significant benefit using N-acetylcysteine (NAC), research has not supported the benefit of NAC for the treatment of children.

Special Problems in Disturbed Children

- All stimulatory behaviors require treatment for the underlying disorder.
- Special behavioral treatment is needed beyond the scope and expertise of the primary care physician.
- When the behavior is severe, institutionalization is often required, and methods of treatment include
  - Aversive behavior modification techniques
  - Use of arm and neck restraints
  - Head helmets
  - Psychotropic medications
  - Psychotherapeutic behavioral programs

WHEN TO REFER

- Persistence of head banging or rocking >3 years.
- Preoccupation with self-stimulating behavior to the point that it interferes with healthy social and emotional interaction.
- Presence of accompanying symptoms, such as decreased socialization or other behavioral problems.
- Behaviors causing tissue damage.
- For hair pulling and twisting, referral to a mental health professional is often warranted to investigate possible underlying causes of tension and anxiety.

FOLLOW-UP

- Weekly visits to the physician for the first month of treatment are important to reinforce the change in behavior.

PROGNOSIS

- Thumb-sucking and nail-biting
  - Only 4% develop motor stereotypies.
  - The probability of malocclusion in children who suck their thumbs appears to be directly related to the age at which the habit is discontinued.
    - Children who cease the habit when they are >6 years generally exhibit some degree of malocclusion when examined at 12 years of age.
    - Thumb-sucking that persists into school age can bring on teasing from peers and criticism from teachers and family, leaving the child with decreased self-esteem and increased psychological distress.
- Masturbation
  - Masturbation will continue as a lifelong pleasurable experience unless suppressed by parents or other adults.
- Hair pulling and twisting
  - Obvious cosmetic damage often results in ridicule by peers and shame for the child.

DEFINITION

- *Septic arthritis,* or *pyogenic arthritis,* is defined as a bacterial infection of the joint.
- Can lead to permanent deformity and disability, particularly in the young child.
- Complications can be minimized by prompt diagnosis and aggressive treatment.

SIGNS AND SYMPTOMS

- Joints of the lower extremities are the most common sites of septic arthritis.
  - The knee is the most affected joint.
  - Rarely, and usually with prolonged bacteremia, ≥1 joint can become infected.
- Common signs include
  - Pain with joint motion or refusal to move an infected joint (most characteristic finding)
  - Swelling
  - Erythema
  - Tenderness
  - Redness of the skin over the joint
    - Can be difficult to detect in a deep joint, such as the hip
  - Limp or refusal to bear weight when a lower-extremity joint is involved
  - Limited range of motion when an upper-extremity joint is involved
    - May result in concerns about a neurologic problem, eg, pseudoparalysis
- Older children and teenagers can usually localize the pain.
  - Pain can be referred to an unaffected joint.
- Signs of acute illness most often accompany the onset of septic arthritis.
  - Fever
  - Malaise
  - Poor appetite
  - Irritability
- In the neonate, systemic signs may be less apparent.
  - Localized signs are usually prominent.
    - Failure to move an infected joint
    - Severe pain associated with passive movement of the affected extremity
    - Significant pain on manipulation of the hip joint during diaper changes

DIFFERENTIAL DIAGNOSIS

- Rheumatologic
  - Typically involves multiple joints.
  - Presentation is often subacute and chronic.
  - Includes juvenile idiopathic arthritis (JIA).
    - Formerly called juvenile rheumatoid arthritis.
    - A diagnosis of exclusion.
    - When children with JIA have high fever and single joint involvement, the diagnosis can be more confusing.
    - In many instances, the diagnosis is made only over time, when
      - Fevers persist.
      - Other joints become involved.
      - No pathogen is isolated in single joint and no response to therapy for a pyogenic infection.
    - The diagnosis of JIA can remain unclear for weeks to months until the course clarifies the chronicity of the disease.
- Transient synovitis
  - Most often affects the hip in young children.
  - Often preceded by recent history of upper respiratory infection, pharyngitis, otitis media, or gastroenteritis.
  - Fever is rare in these cases.
  - Legg-Calvé-Perthes disease must be considered when hip pain is involved.
  - Children with infective arthritis are often very ill from an associated bacteremia; rheumatologic disease is usually more subacute or chronic.
- Reactive or inflammatory arthritis
  - An immunologically induced inflammatory response to a distant infection.
  - Often follows a prior obvious infection.
  - Children can be very ill from associated bacteremia.
- Leukemia
  - Children with leukemia can have
    - Fever
    - Bone pain
  - Examining the bone marrow is often required to confirm diagnosis.
- Isolated neuropathy
  - Can cause decreased movement of a joint but will not be associated with pain or fever
- *Mycobacterium tuberculosis*
  - A history of exposure can direct the diagnosis.
  - Culturing joint fluid must be done on special media.
  - If suspected, perform a tuberculin skin test and order a chest radiograph.
- Lyme disease
  - The child with *Borrelia burgdorferi* will often have a history of erythema migrans.
  - Serologic testing can help confirm diagnosis.

- Knowing the frequency of this pathogen in the pediatrician's area of practice is important.

DIAGNOSTIC APPROACH

- Characteristic signs help suggest the diagnosis.
  - The child holds the infected joint very still to decrease pain.
  - The joint is held immobile by muscle spasm in a position that
    - Maximizes capsular volume
    - Minimizes intra-articular pressure
  - Preferred positions include
    - For the hip, a combination of moderate flexion, abduction, and external rotation
    - For the knee, gentle flexion
    - For the shoulder, adduction against the trunk
- The child may appear entirely well and in no distress as long as the affected joint is undisturbed.
- If the child holds a joint still and has a fever, a septic joint is assumed.

LABORATORY FINDINGS

- Erythrocyte sedimentation rate is typically elevated.
  - May be normal early in the course of infection
- C-reactive protein level is increased.
  - A more sensitive test during initial illness because it increases earlier than the sedimentation rate
- Blood cultures should always be obtained.
  - Blood culture results are positive in ≥40% of children with septic arthritis.
- Other testing may include
  - Titres for Lyme, *Streptococcus,* and other pathogens.
  - Tuberculin test by serum interferon may be appropriate, as in the older child in whom tuberculosis is being considered.
  - Procalcitonin may be found useful as a specific marker in differentiating acute osteomyelitis and septic arthritis from viral and noninfectious inflammatory conditions.
- Examination of joint fluid in pyogenic arthritis.
  - Appearance
    - Generally cloudy or purulent
  - Cell count
    - Leukocyte count >50,000 cells/mcL
    - Predominance of polymorphonuclear cells
  - Gram stain/fluid culture
    - Positive culture results in 50%–60% of cases caused by bacterial infection.
    - Attention to culture technique and special media is required to isolate *Neisseria gonorrhoeae* and *M tuberculosis.*
- Examination of joint fluid in JIA.
  - Can also contain many neutrophils
    - In general, levels are lower than with bacterial infection.
- Joint effusion with a low leukocyte count and normal glucose suggests
  - Arthritis may be caused by a sympathetic effusion from
    - Adjacent osteomyelitis *or*
    - Aseptic arthritis caused by a reactive arthritis, JIA, or other rheumatologic disease
- Serologic testing can help to confirm a diagnosis of Lyme disease.

IMAGING

- Plain radiographs should be obtained to evaluate for fracture or osteomyelitis if the infection has been present for >1 week.
- Ultrasonography can
  - Define the presence of a joint effusion.
  - Detect the capsular distention that accompanies septic arthritis of the hip.
  - Assist the operator in accurate needle placement during diagnostic aspiration.
- Magnetic resonance imaging may be helpful in defining adjacent bony involvement and soft-tissue abscesses, especially in areas of complex anatomy, such as
  - Hip
  - Sacroiliac joint
  - Pelvic bones

DIAGNOSTIC PROCEDURES

- Joint aspiration with a large-bore needle is the most important diagnostic maneuver.
  - Should be performed by an orthopedic surgeon or interventional radiologist skilled in care of pediatric patients.
  - Fluoroscopy or, possibly, ultrasonography may be used to confirm entrance into the relatively inaccessible hip and shoulder joints.
  - Failure to obtain pus from a joint that appears clinically to be infected can be caused by the thickness of pus in the joint.
- Open drainage of the joint may be necessary to confirm diagnosis and treat infection.

TREATMENT APPROACH

- Septic arthritis is an urgent situation and requires consultation among
  - Primary physician
  - Orthopedic surgeon
  - Interventional radiologist
  - Infectious disease specialist
- Empirical therapy with antimicrobial agents appropriate for the likely pathogen should be started urgently after joint aspiration. It is important to send blood and joint fluid for culture before starting antimicrobial therapy.
- Length of treatment is a minimum of 3–4 weeks.
  - Treatment should continue until the clinical response is complete.
  - Treatment will be longer if
    - Concurrent osteomyelitis is present.
    - Most of the course is oral therapy.

SPECIFIC TREATMENTS

Parenteral Antibiotic Therapy

- Most infections are caused by *Staphylococcus aureus.*
  - An effective antistaphylococcal antimicrobial is almost always part of initial treatment.
  - The following antimicrobial is usually sufficient initially.
    - Penicillinase-resistant penicillin (ie, nafcillin or oxacillin) *or*
    - First-generation cephalosporin
  - Broader coverage in which vancomycin should be considered as initial therapy instead of a β-lactam is appropriate
    - For a child with signs of bacteremia and sepsis
    - For a child who lives in an area with a high incidence of methicillin-resistant *S aureus*
- Once a pathogen is identified, narrow therapy to treat the specific organism.
- In a severely ill or immunocompromised child or an adolescent who is thought to be abusing an intravenous drug as the cause of a bacteremia
  - Antibiotics selected empirically should be effective against
    - *S aureus*
    - Enteric gram-negative bacilli
    - *Pseudomonas*
  - Broad-spectrum penicillin, such as ceftazidime, and an aminoglycoside with vancomycin might be empirical therapy, pending final joint and blood cultures.
- Adolescent with possible gonococcal joint infection
  - Should be treated for staphylococci and gonococci until diagnosis is clarified.
  - Cefuroxime or ceftriaxone, perhaps with vancomycin, depending on the specifics of the case.
- Neonate.
  - A first-generation cephalosporin should *not* be used in a neonate as empirical therapy because of
    - Poor cerebrospinal fluid penetration
    - Concern for a bacteremia seeding the central nervous system
- Parenteral antibiotic therapy is continued
  - At least until child is doing well *and*
  - Signs of acute infection have resolved.

Oral Antibiotic Therapy

- Oral therapy can sometimes be used to finish treatment when an organism
  - Has been identified by blood or joint fluid culture *and*
  - An effective oral agent is available.
- Oral antibiotics can be used only if
  - The organism is susceptible to the antibiotic.
  - The social situation guarantees reliably that the antibiotics will be given as directed.
  - The antibiotic does not cause a gastrointestinal disturbance that might interfere with absorption or compliance.
- The antibiotic must achieve therapeutic levels in bone and joint.
- Laboratory test results (eg, erythrocyte sedimentation rate, C-reactive protein level) should be normalized before switching to an oral agent.

Surgical Treatment

- Surgical referral may be required to
  - Aspirate the joint.
  - Reach diagnosis at times.
  - Treat the infection.
- All children with septic arthritis of the hip should be seen emergently by an orthopedic surgeon.
  - They require immediate drainage of the joint.
  - Delay in draining a major joint, such as the hip, is associated with worse outcomes.
  - Open debridement may be required.
- Other infected joints less often require open debridement but should also be evaluated for surgical treatment.
- Repeated aspirations of a joint may be necessary if fluid re-accumulates.

WHEN TO ADMIT

- All children thought to have bacterial infection of a major joint should be hospitalized.

WHEN TO REFER

- Children being evaluated for bone or joint infection should be evaluated by an
  - Orthopedic surgeon *and/or*
  - Infectious disease specialist

COMPLICATIONS

- Pyogenic arthritis constitutes a clinical emergency.
  - Complications of untreated infection include
    - — Dissolution of articular cartilage
    - — Necrosis of the underlying epiphysis
    - — Destruction of the adjacent growth plate
    - — Dislocation of the joint itself
- Possible neuropathies include
  - Septic arthritis of the shoulder: brachial plexus neuropathy.
  - Septic arthritis of the hip: neuropathies of femoral and sciatic nerves.
  - These neuropathies occurring without infection should not be associated with pain or fever.
- Complications can be minimized by
  - Prompt diagnosis
  - Aggressive treatment

PROGNOSIS

- Consequences of bacterial arthritis can be severe.
  - Direct destructive effect of infection.
    - — The host's inflammatory response can add to damage.
  - By increasing intra-articular pressure, intracapsular infection can obstruct blood flow.
    - — May lead to necrosis of the epiphysis and underlying growth plate
  - Untreated joint infection can result in joint instability through destruction of the ligamentous fibers of the capsule.
  - These factors are of special concern for the hip joint in children.

DEFINITION

- The involvement of children or adolescents in sexual activities
  - That they do not fully understand
  - To which they cannot give informed consent
  - That violate the social taboos of families or society
- Includes activities such as
  - Sexual touching of a child's genitals by an adult or adolescent
  - Sexual intercourse between an adult and child
  - Exposing children to pornography
  - Involvement of children in prostitution

SIGNS AND SYMPTOMS

- A physician's concerns about the possibility of sexual abuse result from
  - Reports of specific statements made by the child, usually to a parent or other adult, about uncomfortable experiences (eg, being touched on the genitalia)
  - Reports of specific behaviors of the child (eg, sexualized behaviors with a sibling)
  - Symptoms (eg, encopresis, vaginal discharge, bleeding)
  - Genital or anal injury noted on physical examination
- Clear statements by the child (or occasionally accidental direct observations of the sexual abuse) are the best indicators of sexual abuse.
- Most children who have been sexually abused do not disclose until weeks or months after the occurrence.
- Young children
  - Are most likely to tell a parent or other close adult caregiver about abuse but may lack the necessary vocabulary to describe what happened.
  - May use words of encouragement used by the perpetrator (eg, "We played the hugging game").
  - May describe their experience in a way that is confusing to the adults (eg, "He stuck a knife in my pee-pee").
- Older children
  - Are as likely to tell a peer about abuse as they are to tell a parent.
  - May begin by offering a guarded, vague disclosure (eg, "My uncle kisses too hard").
  - May provide more detail if an adult is told and reacts with appropriate exploratory questions.
  - May be embarrassed.
  - May feel partially responsible.
  - May have experienced pleasurable feelings.
  - May be concerned about threats by the perpetrator (eg, "If you tell your mother, I will punch you"; "If you tell, you know they will think you are a liar").
- Once children realize how upsetting the information is to the family, they may retract the statement.
  - Older children also may feel responsible for holding the family together.
  - If nothing is said, the sexual abuse will continue, but at least the family will be saved.
- Symptoms include
  - Some children may be relatively asymptomatic and be able to function in social settings and in school.
  - Nonspecific symptoms also seen in response to other childhood stresses include
    - Sleep problems
    - Generalized anxiety
    - Suicidal gestures
    - Poor school performance
    - High rates of reported genital soreness and dysuria in girls
  - Sexualized behaviors are more suggestive of sexual abuse.
    - Excessive masturbation
    - Use of adult words associated with sexuality
    - Simulation of sexual intercourse with another child, animal, or doll
  - Physical symptoms are present in only a small percentage.
    - Vaginal pain.
    - Bleeding.
    - Discharge.
      - Uncommon and most likely due to poor hygiene
    - Rectal bleeding.
    - Acute findings, such as genital or anal abrasions, may be more likely to be seen in the emergency department setting.
    - The absence of physical findings does not rule out sexual abuse.
    - Even in adolescents who are pregnant and examined for suspected sexual abuse, physical findings indicating sexual abuse are unusual.
  - Two possible explanations for lack of physical evidence are
    - Penetration does not result in visible tissue damage.
    - Acute injuries occur with penetration but heal completely.

- Normal and abnormal genital and anal anatomic features in prepubertal children and adolescents.
  - Hymen is present in all normally developed newborns.
  - In normal prepubertal girls, hymen shapes are
    - Crescentic.
    - Annular.
    - Fimbriated (or redundant).
    - Often thickened early in life because of the effects of maternal estrogen in utero.
    - In preschool-aged and school-aged girls, hymenal tissue becomes thinner until thickening during puberty from increased estrogen.
  - Normal variations include
    - Hymenal mounds
    - Intravaginal ridges
    - Adhesions of the labia minora

- Findings considered suspicious or suggestive of past abuse include
  - U- or V-shaped clefts (or notches) of the posterior rim (from the 3-o'clock to 9-o'clock positions) of the hymen, which occur in the healing process after an acute laceration.
  - Attenuation or decreased width of the hymenal tissue posteriorly (<1 mm).
  - These findings should persist when the child is examined in the prone, knee-chest position.
- In a study of girls aged 3–8 years with a history of penetrating sexual abuse and girls who denied prior abuse, there were few differences in anatomic findings.
  - A few specific hymenal findings were evident in some of the abused group.
    - Deep notches.
    - Perforations.
    - Transections.
    - Scarring, such as of the posterior fourchette, also indicates previous trauma.
- Previous investigators have considered an enlarged horizontal diameter of the hymen >4 mm to be suspicious in prepubertal children.
  - Studies of normal children have indicated that this demarcation is incorrect and that the size of the opening varies with child's age, different examination techniques, and the child's state of relaxation.
  - A horizontal diameter of >10 mm may concern a physician about the possibility of sexual abuse but should not be used to make a diagnosis.
- Data about normal physical findings in adolescence have been limited.
  - A study compared 3 groups of female adolescents.
    - Those who denied sexual intercourse and used only pads for menses.
    - Those who denied sexual intercourse and used tampons.
    - Those who had experienced sexual intercourse.
    - Median horizontal diameters of the hymenal orifice differed in the 3 groups (1.2, 1.5, and 2.5 cm, respectively); overlap existed.
    - 81% of sexually active teenagers, 11% of tampon users, and 5% of pad users had a complete cleft (or V-shaped notch) between the 2-o'clock and 10-o'clock positions on the hymenal border.
  - A later study used a colposcope for magnification and photographic documentation of hymenal morphologic features.
    - Posterior hymenal notches and clefts were more common (48%) in girls admitting past intercourse than in girls who denied it (3%).
    - The 3% of girls who denied intercourse and had posterior hymenal clefts described a painful first experience with tampon insertion.
    - The mean width of the posterior hymenal tissue was not significantly different between girls who admitted and those who denied past intercourse.
  - Abnormalities of male genitalia caused by sexual abuse are unusual, but acute abrasions, lacerations, or bruises caused by physical abuse can be seen.
  - Acute anal findings, such as lacerations from anal penetration or injury, have been noted.
    - Few systematic studies of perianal findings in chronically abused children have been conducted.
    - Worrisome findings include
      - Thickening of the rugae
      - Distorted anatomy secondary to scarring
      - Dilation >2.0 cm (when the child is in the prone, knee-chest position and no stool is visible in the rectal ampulla)
  - In a study of children with documented anal injuries followed from acute injury to healing, 29 of 31 children healed completely, with scar formation only in the 2 cases requiring acute surgical repair.

- A study of normal prepubertal children highlighted common normal findings that were noted when the child was examined in the prone, knee-chest position.
  - Skin tags in the midline
  - Fan-shaped areas in the midline superiorly
  - Perianal erythema
  - Venous congestion
  - Anal dilation up to 2.0 cm
- Sexually transmitted infection (STI).
  - Children who have been sexually abused may acquire an STI.
  - ~5% of sexually abused children acquire an STI from the perpetrator of the abuse.
  - A 2005 clinical report published by the American Academy of Pediatrics reported *Neisseria gonorrhoeae*, syphilis, or *Chlamydia trachomatis* as diagnostic of sexual abuse in prepubertal children in whom perinatal transmission and rare, nonsexual vertical transmission are excluded.
  - The presence of HIV infection in prepubertal children is diagnostic of sexual abuse in those in whom perinatal and transfusion-related acquisition are excluded.
  - Human papillomavirus (HPV) presents a special case in the evaluation for possible sexual abuse.
    - Vertical transmission is either not a common source of HPV infection or not a source of infection at all.
    - Many preadolescent children acquire HPV from nonsexual horizontal transmission.
      - Autoinoculation if a child has common skin warts
      - Horizontally from non-abusive contact by a person who has common warts
    - The likelihood of sexual abuse as a possible cause increases with age.
    - History and full medical evaluation are important in ascertaining the possibility of sexual abuse in a child with HPV.
- Pregnancy.
  - Pubertal female victims are at risk for pregnancy from sexual abuse.
  - Adolescents who become pregnant from sexual abuse often try to hide the pregnancy and can be extremely reluctant to name the perpetrator.
  - If the perpetrator is a family member, the psychological consequences for the adolescent and non-offending family members can be particularly complex and debilitating.

DIFFERENTIAL DIAGNOSIS

- Sexual abuse should be distinguished from sexual play and exploration by young children or sexual activities between consenting adolescents.
- Some of the physical findings that can be seen in sexually abused children are nonspecific, such as erythema of the vulva or introitus.
- Bruises.
  - In the genital or anal area should raise concern about physical abuse.
  - Consider medical conditions, such as bleeding disorders, if more widespread.
- Straddle injuries.
  - Can affect genitalia.
  - Usually witnessed, so history is clear.
  - Usually unilateral or anterior.
  - Produce obvious bruising and swelling of external genitalia.
  - Involvement of hymen is unusual.
- Lichen sclerosus.
  - Dermatologic condition that may exhibit genital soreness and subependymal hemorrhages
  - Usually affects vulva and perianal region
  - Hourglass appearance, with areas of subependymal hemorrhage, decreased pigmentation, and tissue friability
- Urethral prolapse.
  - Can produce vaginal bleeding and dysuria.
  - Abnormalities noted on physical examination might appear as trauma from sexual abuse.
- Streptococcal infection.
  - Causes marked redness of the perianal region and vaginal discharge
- Foul-smelling vaginal discharge.
  - Consider foreign body.
- Challenging to differentiate abnormalities caused by sexual abuse from normal variations.
  - In one study, the most experienced physicians were more likely to agree with the ratings of an expert panel on sexual abuse.
  - Another study showed that history provided in a simulated case influenced physicians' interpretations of physical findings.
- False allegation.
  - Should be considered in the differential.
  - Although false allegations seem to be uncommon, controversy exists about
    - Accuracy of young children's memory
    - Circumstances where leading questions may result in false reports

- Carefully consider false allegations if
  - The child has a serious mental health problem.
  - The child's statements lack detail.
  - The child's statements have important inconsistencies or seem rote in nature.
- If the child is part of a bitter dispute between the parents (eg, a custody fight), a false allegation, although rare, must be considered.

DIAGNOSTIC APPROACH

- The pediatrician may learn about suspected sexual abuse from
  - Parents
  - Direct statements from the child
  - Abnormalities noted on physical examination or laboratory tests
- When sexual abuse is suspected, an important decision point is whether mandatory reporting requirements are met.
  - In most states, the requirement to report is based on the level of reasonable suspicion.
- 5 important clinical steps for initial evaluation.
  - First, decide how much history to obtain directly from the child.
    - Many locales can provide timely, subspecialty-level evaluation for suspected sexual abuse.
    - Only a minimal history or, in some circumstances, no direct history may be necessary because the child will be interviewed by a specially trained forensic interviewer (with observers from police and child protective services).
  - Second, decide on the extent of the physical examination to be performed and whether collection of laboratory or forensic data is indicated.
    - A brief external examination to rule out acute trauma can be performed with referral for emergency care only in the event that acute trauma is present.
    - If the child has symptoms of an STI, obtain appropriate laboratory tests.
    - If the pediatrician evaluates the child within 72 hours of the last occurrence of sexual abuse, forensic evidence may need to be collected in an emergency department.
    - Advise parents to reserve in a paper bag any unwashed clothing or bedding with which a suspected perpetrator may have been in contact.
  - Third, carefully document in the medical record any collected information.
  - Fourth, meet with non-offending parents (and the child, if old enough) to explain that a report will be made to child protective services and that an investigation will be conducted in the community.
  - Fifth, arrange follow-up with the family to offer ongoing support during the ensuing forensic evaluation.
- Many communities have children's advocacy centers (CACs), multidisciplinary teams (MDTs), or both, that provide a coordinated approach to evaluation of suspected sexual abuse.
  - CACs provide comprehensive, multidisciplinary assessments of abused children in an environment designed to be neutral and child friendly.
  - CACs may house needed mental health services for children and families.
  - MDT members can include representatives from the local police, prosecutors' office, and protective services and experts in interview and examination.
  - MDT meetings provide an opportunity for discussion of specific cases and coordinated investigative and treatment efforts as well as a forum for community-wide efforts in prevention and early detection.
  - Shared goals of CACs and MDTs are minimizing secondary trauma experienced by the child and family resulting from the investigation.
- As part of the evaluation, subspecialty physicians should consider alternative explanations, including an unintentional injury (or accident), a medical problem, or a false allegation.
- Because evaluations for suspected sexual abuse usually include the child protection and legal systems, care should be taken to provide an unbiased assessment and one that provides documentation that can be reviewed by professionals outside the medical system.
- History.
  - Should include
    - Events that led to the evaluation
    - Child's health status and level of development
    - Family's strengths and weaknesses
  - Ask the parents (or guardians)
    - What the child has said
    - How the child reacted when telling about the abuse
    - Whom the child told

- Obtain information about
  - Changes in behaviors or attitudes toward a specific person or situation
  - Recurrent fears or nightmares
  - Sexualized behaviors
  - Specific symptoms, such as vaginal bleeding or discharge, dysuria, anal bleeding, constipation, and encopresis
  - Where the child spends time and who cares for the child
- Try to determine
  - Who the alleged perpetrator is
  - The relationship with the child
  - The amount of time spent with the child
- In preparation for interviewing the child, know the child's developmental history, eg, whether a language delay is present.
- Family history should include
  - Information about the parents' physical and mental health, including a history of sexual abuse during childhood
  - Health and developmental status of the siblings
  - The presence of family violence, substance abuse, or recent stresses
  - The resources and supports available to the family
- Understand how family members view the allegations and how they have reacted.
- Because allegations that arise during a custody fight between parents are often difficult to sort out, determine
  - Whether the parents are separated or divorced
  - Custody arrangements
  - Visitation schedule
  - Any disputes about custody or visitation
- Distinguish whether allegations of abuse occurred before the separation or divorce, during the process of separation and divorce, or after the divorce had been finalized.
- A child who is old enough to be interviewed directly should be asked about what may have happened.
- Pediatricians should perform minimal interviewing to obtain enough information to warrant a report to child protective authorities.
- Trained, forensic interviewers can then obtain a full disclosure that can be used as evidence in any legal proceedings stemming from the allegations.
  - The recent development of forensic interview protocols, such as the National Institute of Child Health and Human Development Investigative Interview Protocol, allow for
    - Standardization of techniques
    - More elicited detail
    - Minimization of trauma to the interviewed child
  - This interview or series of interviews should be conducted with the child alone, if possible.
  - The interviewer should
    - Be comfortable and skilled at interviewing young children about the possibility of sexual abuse.
    - Use simple questions.
    - Be aware of the child's nonverbal responses and direct statements.
  - Leading questions, such as, "Didn't he touch your pee-pee?" should be avoided.
  - Non-leading questions are preferable, such as, "Can you tell me what happened?" or "Where did he touch you?"
  - In many instances children are reluctant to talk because of a variety of reasons, including fear and embarrassment.
  - Questions with forced choice responses, such as, "Was it your mother or father or teacher who did that?" or "Was his pee green or pink or white?" can be helpful.
  - To help young children during the interview, anatomic drawings or anatomically correct dolls have been used.
    - Considerable controversy surrounds the sexual nature of the dolls and whether use suggests to children that they can talk about sex, thus leading to false allegations.
    - Research indicates that few non-sexually abused children respond in sexual ways and that the dolls can be helpful to children in describing what happened.
  - Some older children who have difficulty verbalizing acts of sexual abuse may be able to draw pictures of or write out a description of what occurred.
- Physical examination.
  - The purpose of physical examination is to determine the presence or lack of
    - Signs of physical abuse or neglect
    - Anogenital injuries consistent with or suggestive of sexual abuse
    - Conditions that need medical treatment

- The examination provides an opportunity to reassure the child and family about the child's physical condition.
- In premenarcheal girls, the genital examination is performed best in the supine and the prone, knee-chest positions; a speculum is seldom used.
- To visualize the hymen
  - Labial separation (separating and pulling posteriorly at an angle of 45°)
  - Labial traction (gently pinching the labia and pulling out and toward the examiner)
- Evaluations conducted in specialty centers rely on colposcopic anogenital examination to provide 5- to 30-fold magnification and documentation.
- A study comparing examinations with and without colposcope indicated that >95% of physical findings can be detected without its use.
- A handheld magnifying lens that provides 2.5- to 3-fold magnification or an otoscope (without a speculum) can provide reasonably good magnification.

- Documentation.
  - Should include
    - Direct quotations from parents and child
    - Clear description of the findings from the physical examination, with sketches, if necessary
  - In many states, information about suspected sexual assault is recorded on a specific form.
  - A video recording of the child's interview and videotape or photographs of the examination provide additional information.
  - Label video recordings with the date, child's name, physician's name, and child's medical record number.

LABORATORY FINDINGS

- When the child is at risk for acquiring an STI, appropriate tests should be obtained for
  - Gonorrhea
  - Herpes simplex
  - Trichomonas
  - Bacterial vaginosis
  - Chlamydia
  - Syphilis
  - HIV
  - Hepatitis B and C
- Cultures for *N gonorrhoeae* and *C trachomatis* have been considered the gold standard.
  - Newer tests, such as nucleic acid amplification tests (NAATs) that detect the presence of the organism DNA or RNA, may be run on urine samples as opposed to vaginal or urethral swabs.
  - Data on use of these tests in prepubertal children are scarce.
  - The prevalence of these infections in children is very low.
  - As NAATs are increasingly used, their importance clinically and legally can be expected to increase.
  - The Centers for Disease Control and Prevention suggests using NAATs to detect *N gonorrhoeae* and *C trachomatis* because of the tests' increased sensitivity over culture.
- For a child who has a vaginal discharge, additional studies may be performed to test for trichomonal or bacterial vaginosis.
- Serologic samples may be analyzed for HIV, hepatitis B and C, and syphilis.
- The decision to screen for these infections in prepubertal children should be guided by
  - Nature of the sexual contact
  - Signs and symptoms
  - Presence of another STI
  - Risk status of the perpetrator
  - Family wishes
  - Discretion of the medical provider
- Studies have attempted to determine which children should be tested for STIs.
  - In a review of 2,731 preteens who had vaginal cultures, 84 (3.1%) had gonorrhoeae, and 80 of these had a vaginal discharge.
  - No data are available to help determine which children should have cultures taken from genitals, throat, and anus.
  - If the child has evidence of one STI, conducting a full range of tests for other STIs would then be reasonable.
- Forensic evidence.
  - An important component of evaluating victims of sexual abuse.
  - When an adolescent is evaluated within 72 hours of an episode of suspected sexual abuse, appropriate forensic information, such as swabs to detect semen, should be collected.
  - Epidemiologic study of forensic evidence findings in prepubertal victims of sexual abuse suggest that the collection of this evidence has a low yield.

- Swabbing a child's body for evidence is, therefore, indicated within the 24-hour period immediately after an acute sexual assault.
- Clothing and linens from sexually abused children provide a significantly higher yield of forensic evidence after an acute sexual assault than samples taken directly from the child.

- In pubertal girls, a pregnancy test may be necessary.

TREATMENT APPROACH

- Management of children who are suspected of having been sexually abused includes
  - Appropriate medical care
  - Reporting to protective services
  - Ensuring mental health services for the child and family
- Counseling about implications of infections, such as HPV or HIV, may be necessary.
- Surgical repairs of genital or anal injuries may be necessary.
- Adolescents may need counseling about terminating a pregnancy resulting from sexual abuse.
- When abnormalities are noted on the physical examination, offer reassurance that these likely will heal and be of little functional importance.
- Physicians who suspect sexual abuse are mandated to report findings to the state's child protection agency.
  - Sexual assault is a criminal offense and the local police also participate in the investigations.
  - Issues that need to be considered include
    - To what extent children should be interviewed further, by whom, and in what setting
    - Where children should go to ensure their safety
    - Whether other children in the home need evaluation
  - The period after the child's disclosure can be emotionally upsetting to everyone and especially confusing to the child.
- Family issues.
  - Family members may blame themselves and be furious at the suspected perpetrator.
  - If the abuser is a relative, the family may be divided.
  - If the abuser is in the immediate family, the psychological issues are even more complicated.
- The physician can be helpful by
  - Maintaining contact with the family
  - Advocating for a reasonable approach by protective services (eg, having the alleged abuser leave the home rather than place the child in foster care)
  - Helping the family to recognize and discuss emotional issues
- When a child discloses sexual abuse, a chain of events is set in motion that has immediate and often distressing consequences.
  - What was once a secret for the disclosing child becomes a very public and emotionally charged event.
  - Children feel guilty for causing this upheaval and must endure potentially terrifying interactions with child protective services and law enforcement.
  - Parents are often overwhelmed by their own reactions; intense anger, fear, blame, and helplessness can cause acute distress.
- Counseling.
  - Most sexually abused children and their parents need short- or long-term counseling.
  - A cognitive behavioral treatment model that focuses specifically on the sexual abuse of the child and involves the child and non-offending parents has improved children's functioning after sexual abuse.
  - The presence or absence of parental support is directly correlated with children's functioning, even as long as a year after disclosure.
- Criminal justice system.
  - Because sexual abuse of a child is a criminal offense, the child and family are often involved in the criminal justice system.
  - Most cases do not actually result in a trial in criminal court.
    - Lack of clear evidence that abuse has occurred
    - Young age of the victim
    - Confession of the perpetrator
    - Willingness of the perpetrator to plea bargain
  - In ~3%–5% of cases, a criminal trial is held in which the child actually testifies.
  - Sexual abuse cases sometimes are tried in family court when allegations of sexual abuse occur as a part of a divorce or custody proceeding or in juvenile court when protective services are concerned about the child's safety in the home.

PROGNOSIS

- Sexual abuse can have a long-lasting and devastating effect.
- Domains of affected functioning include the survivor's
  - Emotional state (eg, depression, anxiety, suicide)
  - Sense of self (eg, feeling worthless or powerless, viewing one's self as a victim)
  - Relationships with others (eg, setting poor boundaries, being promiscuous, using inappropriate sexual behaviors, mistrusting others)
- Important targets for long-term treatment include
  - Self-blame for allowing the abuse to happen
  - Sexuality and sexual awareness
  - Poor self-esteem and feelings of powerlessness
  - Mistrust of adults
- Because of changes in the family, the child has to come to terms with the losses created by the disclosure and the upset and anger in the family.
- Teenage girls and young women seem to be at an increased risk for
  - Eating disorders
  - Multiple personality disorder
  - Posttraumatic stress disorder
  - Pregnancy at young age
- Men who were sexually abused as children are
  - At increased risk for mental health or substance abuse problems
  - More apt to perpetrate sexually coercive acts, including victimizing children sexually

PREVENTION

- Attempts to prevent sexual abuse have been directed toward developing programs to teach children, usually at school, about good and bad touches and what to do if bad touches occur.
- Children as young as 4–6 years can learn and retain these concepts, at least over a short period.
- Evaluations have not been able to provide conclusive evidence that such programs have resulted in the prevention or earlier recognition of sexual abuse.

DEFINITION

- Sexually transmitted organisms
  - *Campylobacter* species
  - *Chlamydia trachomatis*
  - Cytomegalovirus
  - *Entamoeba histolytica*
  - *Giardia intestinalis*
  - Hepatitis A, B, and C
  - Herpes simplex virus (HSV) types 1 (HSV-1) and 2 (HSV-2)
  - HIV
  - Human papillomavirus (HPV)
  - Molluscum contagiosum (papovavirus)
  - *Mycoplasma genitalium*
  - *Mycoplasma hominis*
  - *Neisseria gonorrhoeae*
  - *Phthirus pubis* (pubic lice)
  - *Salmonella* species
  - *Sarcoptes scabiei* (mites)
  - *Shigella* species
  - *Treponema pallidum*
  - *Trichomonas vaginalis*
  - *Ureaplasma urealyticum*

SIGNS AND SYMPTOMS

Signs and Symptoms, by Sex

- Boys
  - Dysuria, discharge, urethral itching (urethritis)
  - Scrotal pain, swelling (epididymitis)
  - Rectal discharge, tenesmus, anorectal pain (proctitis, proctocolitis, colitis)
    - Usually seen in adolescents who practice anal receptive intercourse or oral-anal contact
- Girls
  - Mucopurulent cervicitis
  - Vaginitis (vaginal discharge)
  - Dysuria, urgency, frequency
  - Right upper quadrant abdominal pain
  - Pelvic inflammatory disease (PID) (low abdominal pain)
  - Bleeding between periods (cervicitis) or a heavier, more prolonged period (PID)
- Both sexes
  - Dermatitis, especially
    - Generalized papulosquamous (secondary syphilis)
    - Papular with central umbilication (molluscum contagiosum)
    - Localized pubic itching, or localized itching involving the webs of fingers and the wrists (*P pubis*, pubic lice, or *S scabiei*, mites)
    - Erythematous macules turning pustular or necrotic, accompanied by tenosynovitis (disseminated gonococcal infection [DGI])
  - Genital ulcers (single or multiple)
  - Genital warts
  - Hepatitis A virus, hepatitis B virus, or hepatitis C virus infection
  - Lymphadenopathy, especially inguinal or generalized (associated with HIV)
  - Persistent pharyngitis
  - Septic arthritis

Specific Agents

- *C trachomatis*
  - Symptoms generally develop 1–3 weeks after infection.
  - Male adolescents may report
    - Only mild dysuria or itching at terminal urethra
    - Scanty, mucoid discharge that is easily ignored and may disappear without treatment
  - Dysuria can be the primary manifestation.
  - Female patients may report spotting between periods as a result of cervicitis.
  - If infection has spread to the upper genital tract, female patients may report low abdominal pain or right upper quadrant pain (Fitz-Hugh–Curtis syndrome).
  - Infections in teenaged girls and teenaged boys are often asymptomatic.
  - At pelvic examination, clues include
    - Presence of mucopurulent discharge from the cervical os (known as *mucopus*)
    - Cervical erythema
    - Friability
- *N gonorrhoeae*
  - Symptoms are similar to those of *C trachomatis*.
  - Men tend to have more pronounced symptoms.
    - More severe dysuria
    - Greater amount of and more purulent discharge
  - Pharyngitis and proctitis.
  - Organism may become blood borne and lead to the so-called arthritis-dermatitis syndrome, DGI.
    - Strains of *N gonorrhoeae* that lead to DGI characteristically tend to cause few genital symptoms.
    - Patients develop fever (not always) and may have anorexia, malaise, or both.

  - Skin lesions then appear, generally distributed on extremities (arms more often than legs).
    - Lesions appear as erythematous macules <5 mm in diameter, and then become pustular and occasionally hemorrhagic or necrotic.
    - Lesions are most often near the small joints of the hands and feet.
  - Tenosynovitis tends to occur over extensor and flexor tendons of hands and feet.
  - Once tenosynovitis and dermatitis clear, patients develop polyarthralgia but usually seek care only when an oligoarthritis develops.
    - Knee is the most commonly infected joint.
    - Followed by the elbow, ankle, and small joints of the hands and feet.

- HPV
  - Visible warts usually develop within 6 weeks to 8 months after infection, but the incubation period may be longer.
  - Typical pedunculated warts with keratotic and irregular surfaces are easy to recognize.
    - Warts may also be flat and more difficult to detect.
    - Use of a handheld magnifying glass or colposcope is extremely helpful.
  - Among male adolescents, warts are usually seen on the penile shaft, prepuce, frenulum, corona, and glans but may also be present on the skin of the scrotum and anus.
    - Occasionally, warts are seen at the urethral opening.
  - Among female adolescents, the posterior vaginal introitus, labia minora, and vestibule are most common, but warts can be seen anywhere on the external or internal genitalia.
  - Perianal warts can be seen even in women who have not had anal intercourse.
  - Subclinical disease is most likely to occur on the cervix.
- HSV
  - In primary infection, symptoms usually occur 2–20 days after sexual exposure.
  - Because primary infection represents the first episode of infection with a particular virus type, systemic symptoms, such as fever, malaise, and headache, are common.
  - ~50% of patients have tender inguinal lymphadenopathy.
  - Burning or itching occurs at the site of inoculation, followed by erythema and development of discrete vesicles.
  - Vesicles first contain clear fluid but rapidly form pustules with an erythematous base.
  - Patients typically may have 15–30 vesicles, each full of infectious viral particles.
  - Female adolescents: Lesions are located on the vulva, cervix, clitoris, or perineum.
  - Male adolescents: Lesions may occur on the penile shaft, glans, or prepuce.
  - Infection can involve the urethra, leading to dysuria or urinary retention.
  - Vesicles can be seen on the thighs, buttocks, groin, or perianal region as a result of autoinoculation or anal receptive intercourse.
  - After 2–4 days, pustules break open and coalesce to form wet ulcers (usually prompting patients to seek care).
  - New lesion development peaks at 7–11 days, but within 20 days, all have crusted over and pain and other symptoms have disappeared.

Sexually Transmitted Infections (STIs)/ Syndromes Associated With STIs

- PID
  - Suggestive of PID.
    - Presence of a new vaginal discharge (or a change in odor, color, or amount)
    - Abnormal menstrual bleeding (increased or prolonged; occurring at the wrong time in the cycle)
    - Dyspareunia
  - Other symptoms include
    - Dysuria
    - Dysmenorrhea (usually more severe than normal)
    - Nausea
    - Vomiting
    - Diarrhea
    - Fever (<50% of patients)
    - Malaise
  - Signs may include
    - Pain on movement of the cervix and endometrial or adnexal tenderness, or both
  - If infection involves capsule of the liver, right upper quadrant tenderness may be elicited.
  - With extensive infection, signs of peritonitis, particularly rebound tenderness, are present.
  - Palpation of an adnexal mass suggests a coexisting tubo-ovarian abscess.
  - Mucopus visible in the cervical os strongly suggests infection, but absence does not rule out diagnosis.

- Syphilis
  - Typical chancre of syphilis develops at the site of intimate sexual contact ~2–3 weeks after exposure.
    - Lesion varies in size from a few millimeters to a few centimeters, is painless, has a clean base, and has sharply demarcated, indurated borders.
    - Multiple ulcers may be present.
    - Because the ulcer is painless, its appearance in the vagina or rectum or even in the mouth is likely to go unnoticed.
    - While the ulcer is present, the exudate overlying it is highly infectious.
  - Lymphadenopathy is usually present, often bilaterally.
  - Secondary syphilis.
    - Rash appears 4–10 weeks after chancre appears in an untreated patient.
    - Rash and chancre may coexist.
    - Constitutional symptoms, such as fever, malaise, sore throat, and generalized lymphadenopathy, may be present.
    - Rash is typically papulosquamous but can be macular or pustular.
    - Initially, rash involves trunk and flexor surfaces of arms but then spreads to the entire body, including palms, soles, and mucous membranes.
    - Annular papules can appear on the face and can resemble impetigo or eczema.
    - In some cases, moist, fissured papules or raised, thickened papules (condyloma lata) are seen; both are highly infectious.
    - Possible loss of scalp or eyebrow hair.
    - Rash disappears spontaneously 3–12 weeks after appearance; at this point, the patient is classified as having latent syphilis.
- Perihepatitis (Fitz-Hugh–Curtis syndrome)
  - Violin-string adhesions between the liver and anterior abdominal wall, localized peritonitis of liver's anterior surface, upper abdominal pain and tenderness.
  - Onset of upper abdominal pain usually follows (but can also precede) the onset of lower abdominal pain.
  - Pain generally occurs on the patient's right side and can radiate to the shoulder.
- Epididymitis
  - Acute or subacute onset of unilateral scrotal pain.
  - Adolescent boys may report testicular pain.
  - Preceding symptoms may include urethral discharge and dysuria but may be so mild that they are easily ignored.
  - Fever may be present.
  - At physical examination, tenderness may occur on palpation of the epididymis, but the testicle may also be slightly tender.
  - Hydrocele may be present, and the spermatic cord may be swollen and tender.
  - Urethral discharge may or may not be present.
- Enteric infections
  - Symptoms of proctitis and proctocolitis include anorectal pain, tenesmus, constipation, and anal discharge.
  - Patients with proctocolitis or enteritis have diarrhea.
  - Enteritis: Symptoms are usually limited to abdominal pain and diarrhea; other symptoms of proctitis and proctocolitis are absent.
- Cervicitis
  - Characterized by purulent or mucopurulent discharge from endocervical os or by significant endocervical bleeding (or both), induced when a swab is introduced into the os

DIFFERENTIAL DIAGNOSIS

Anatomic Area[1]

- Urinary tract
  - Cystitis
  - Pyelonephritis
  - Urethritis
  - Other
- Gastrointestinal tract
  - Appendicitis
  - Constipation
  - Diverticulitis
  - Gastroenteritis
  - Inflammatory bowel disease
  - Irritable bowel syndrome
  - Other
- Reproductive tract
  - Acute PID
  - Cervicitis
  - Dysmenorrhea (primary or secondary)
  - Ectopic pregnancy
  - Endometriosis
  - Endometritis
  - Mittelschmerz
  - Ovarian cyst (torsion, rupture)
  - Pregnancy (intrauterine, ectopic)
  - Ruptured follicle
  - Septic abortion

- Threatened abortion
- Torsion of adnexa
- Tubo-ovarian abscess

Specific Agents

- *C trachomatis*
  - Profuse, purulent discharge should raise the possibility of *N gonorrhoeae* coinfection or of this being the single causative agent.
  - Unless a thorough history is obtained, combination of dysuria and right upper quadrant or right flank pain might lead to the erroneous diagnosis of pyelonephritis.
  - Lower abdominal pain suggests the possibility of PID.
  - Vaginal discharge is more likely to indicate presence of another infection.

STIs/Syndromes Associated With STIs

- PID[2]
  - Symptoms resembling PID most often occur in patients with diseases of the urinary tract (eg, pyelonephritis) or gastrointestinal tract (eg, appendicitis).
  - Clinical diagnosis of PID has a positive predictive value for salpingitis of 65%–90%.
    - Positive predictive value is higher for adolescents and in clinical settings with high prevalence of STIs (eg, chlamydia, gonorrhea).
  - Signs and symptoms can be nonspecific, and the only sure method of diagnosis, laparoscopy, is not a routine diagnostic procedure in the United States.
  - To avoid misdiagnosis, primary care physicians must
    - Maintain a high index of suspicion.
    - Obtain an extensive history.
    - Perform a thorough physical examination.
  - More elaborate diagnostic evaluation is often needed; incorrect diagnosis and management might cause unnecessary morbidity.
  - Additional criteria to enhance specificity of minimal criteria and support a diagnosis of PID include
    - Oral temperature >38.3°C (101°F)
    - Abnormal cervical or vaginal mucopurulent discharge
    - Abundant leukocytes on saline microscopy of vaginal secretions
    - Increased erythrocyte sedimentation rate
    - Increased C-reactive protein level
    - Laboratory documentation of cervical infection with *N gonorrhoeae* or *C trachomatis*
  - Other diagnoses to consider include
    - Cervicitis
    - Dysmenorrhea (primary or secondary)
    - Ectopic pregnancy
    - Endometriosis
    - Endometritis
    - Mittelschmerz
    - Ovarian cyst (torsion, rupture)
    - Pregnancy (intrauterine, ectopic)
    - Ruptured follicle
    - Septic abortion
    - Threatened abortion
    - Torsion of adnexa
    - Tubo-ovarian abscess
- Latent syphilis
  - Early latent syphilis cannot be reliably distinguished from late latent syphilis solely on the basis of nontreponemal titers.
  - All patients with latent syphilis should have a thorough examination of all accessible mucosal surfaces to evaluate for internal mucosal lesions.
    - Oral cavity
    - Perineum in women
    - Perianal area
    - Underneath foreskin in uncircumcised men
- Epididymitis
  - In adolescents, rule out testicular torsion.
- Cervicitis
  - Women with cervicitis should be carefully evaluated for
    - PID
    - Trichomonas and bacterial vaginosis
    - Chlamydia
    - Gonorrhea
- Urethritis
  - Differentiation between *U urealyticum* (which does seem to be capable of causing urethritis) and *Ureaplasma parvum* (which does not) may help to clarify the etiology of nongonococcal, non-chlamydial urethritis.

DIAGNOSTIC APPROACH

- When an adolescent seeks care for symptoms and clinical findings that might be caused by an STI, the physician must proceed with appropriate diagnostic tests or therapy, even though the history may seem to exclude such a cause.

- Most sexually active teenagers will be truthful when
  - Questioned respectfully without parent or guardian present
  - Given appropriate guarantees about confidentiality
- Increasingly widespread availability and use of nucleic acid amplification test (NAAT) to diagnose *C trachomatis* and *N gonorrhoeae* infections represent major advances.
  - Benefits include
    - More sensitive than culture and previous generations of nonculture tests.
    - Do not require recovery of viable organisms.
    - Can be performed on urine specimens or self-obtained vaginal swabs.
  - By eliminating or reducing the need for invasive testing, NAAT may expand the number of at-risk youth who are screened.
  - A urine NAAT is the preferred test for detecting chlamydia among males.
  - Self-obtained vaginal swabs are the preferred method for chlamydia detection among asymptomatic females; sensitivity exceeds that of urine specimens and is equal to or better than cervical swabs.

LABORATORY FINDINGS

Specific Agents

- *C trachomatis*
  - Gram stain of cervical tissue will reveal the presence of 10–30 polymorphonuclear white blood cells (WBCs) per oil-immersion field.
  - NAAT is the diagnostic assay of choice.
- *N gonorrhoeae*
  - Organism can be grown from
    - Urethral or cervical discharge
    - Swabs of the vagina, cervix, urethra, pharynx, or rectum
    - Urine sediment (in many cases)
  - In the past, diagnosis rested on culture or classic findings of WBCs and gram-negative intracellular diplococci in Gram stains of discharge or material obtained from a urethral swab.
  - Even under ideal conditions, organism can be difficult to grow; physicians should be familiar with yield from the laboratory they use.
  - In men, typical Gram stain from a urethral discharge is diagnostic.
  - In women, sorting out gram-negative organisms that truly are intracellular versus those that may be overlying or near cells is more difficult.
    - When ≥8 pairs of such diplococci are seen in ≥2 polymorphonuclear leukocytes, culture result will be positive 96% of the time.
  - Centers for Disease Control and Prevention (CDC) now recommends NAAT for detection of *N gonorrhoeae.*
    - More sensitive than culture
    - Eliminates pelvic examination or swabbing urethral meatus
- HSV
  - Cell culture and polymerase chain reaction (PCR) are preferred tests for detection.
  - Sensitivity of culture declines as lesions begin to heal and is low for recurrent lesions.
  - PCR assays are more sensitive than culture, but negative culture or PCR test result does not preclude herpes infection.
  - Recurrence rates for genital HSV-1 and HSV-2 differ significantly; testing should be performed whenever a patient presents with new-onset genital herpes.

STIs/Syndromes Associated With STIs

- PID
  - Acute-phase reactants lack the necessary sensitivity and specificity to help diagnose PID.
  - Although 60%–80% of patients have an increased WBC count, sedimentation rate, or C-reactive protein level, so do 20%–50% of patients with abdominal pain without PID.
  - Test results obtained from cervical specimens do not necessarily reflect the nature of the endometrial or tubal infection.
  - Many organisms thought to play a role in PID are difficult to grow in culture.
  - Studies that have been performed emphasize the polymicrobial nature of the infection.
    - *N gonorrhoeae, C trachomatis,* or both are recovered from ~25%–75% of adolescents and young adults with PID.
    - Facultative and anaerobic bacteria, as well as organisms associated with bacterial vaginosis, have been recovered from various points in the upper genital tract of women who have PID.

- Syphilis
  - When the chancre is present, dark-field examination of non-bloody exudate should be performed by a dark-field microscopy expert.
    - If test is done on 3 successive days, the likelihood of obtaining a positive result from an infected individual is extremely high.
    - If results of all 3 tests are negative, reconsider diagnosis of primary syphilis.
  - If dark-field examination is unavailable, obtain serologic test for syphilis.
    - 2 types.
      - Nontreponemal (Venereal Disease Research Laboratory [VDRL] test and rapid plasma reagin [RPR])
      - Treponemal (eg, fluorescent treponemal antibody absorbed test)
    - Some laboratories are initially screening samples using a treponemal test rather than performing the nontreponemal test first.
    - Using only one type of test is insufficient because both tests have limitations.
      - False-positive nontreponemal results may be obtained in individuals with autoimmune disorders.
    - Symptoms of syphilis may not be consistently present in everyone infected; most adolescents infected with syphilis will be identified only through routine serologic screening.
      - Testing at-risk youth is important.
- Perihepatitis (Fitz-Hugh–Curtis syndrome)
  - <50% of patients have mildly increased liver enzyme levels.
- Epididymitis
  - Supportive laboratory evidence includes
    - Positive leukocyte esterase test result on first-catch urine specimen (the first 20 mL of urine voided) or presence of >10 WBCs per high-power field if first-catch urine specimen is spun down and sediment examined *or*
    - Gram stain of urethral secretions showing >5 WBCs per oil-immersion field
      - If Gram stain also shows WBCs containing intracellular gram-negative diplococci, *N gonorrhoeae* should be considered causative.
- Enteric infections
  - Proctocolitis: Fecal leukocytes may be detected on stool examination, depending on the pathogen.
  - Proctitis: Evaluate patient for infection with HSV (PCR or culture), *N gonorrhoeae* (NAAT or culture), *C trachomatis* (NAAT), and *T pallidum* (dark-field if available and serologic testing).
  - If *C trachomatis* test result on rectal swab is positive, a molecular test PCR for lymphogranuloma venereum (LGV) should be performed if possible.

Sexual Assault

- The initial examination of a sexual assault victim can include
  - NAAT for detection of *C trachomatis* and *N gonorrhoeae*
  - Baseline testing for syphilis, hepatitis B, and HIV
  - Vaginal wet mount to look for evidence of bacterial vaginosis and to obtain specimens for detection of trichomoniasis.

DIAGNOSTIC PROCEDURES

- Patients with proctitis (the distal 10–12 cm of the rectum) should be examined with anoscopy.
- Patients with anal warts and warts on the rectal mucosa can benefit from inspection of the rectal mucosa by digital examination or anoscopy.
- Primary and secondary syphilis.
  - After the newborn period (≥1 month), examine the cerebrospinal fluid (CSF) of children with syphilis to detect asymptomatic neurosyphilis.
  - Review birth and maternal medical records to assess whether congenital or acquired.
- Latent syphilis.
  - After the newborn period, examine the CSF of children with syphilis to exclude neurosyphilis.
  - Review birth and maternal records to assess whether congenital or acquired.

TREATMENT APPROACH

- Empiric treatment of PID should be initiated in sexually active young women and others at risk for STIs if
  - They are experiencing pelvic or lower abdominal pain.
  - No cause for illness other than PID can be identified.
  - ≥1 of the following minimal criteria are present on pelvic examination:
    - Cervical motion tenderness
    - Uterine tenderness
    - Adnexal tenderness

- Requiring that all 3 of the minimal criteria listed here be present before initiating antibiotic treatment might result in insufficient sensitivity for diagnosing PID.

SPECIFIC TREATMENTS[3]

C trachomatis

- Coinfection with *C trachomatis* often occurs among patients who have gonococcal infection; therefore, presumptive treatment of such patients for chlamydia is appropriate.
- The following recommended treatment regimens and alternative regimens cure infection and usually relieve symptoms:
- Recommended.
  - Azithromycin 1 g orally in a single dose *or*
  - Doxycycline 100 mg orally twice daily for 7 days
- Alternative regimens.
  - Erythromycin base 500 mg orally 4 times daily for 7 days *or*
  - Erythromycin ethylsuccinate 800 mg orally 4 times daily for 7 days *or*
  - Levofloxacin 500 mg orally once daily for 7 days *or*
  - Ofloxacin 300 mg orally twice daily for 7 days
- Other considerations.
  - Azithromycin.
    - Should always be available to treat patients for whom compliance with multidosing is questionable.
    - Studies have raised concerns about efficacy for rectal infection.
    - Although clinical significance of oropharyngeal infection is unclear and routine oropharyngeal screening for *C trachomatis* is not recommended, evidence suggests oropharyngeal *C trachomatis* can be sexually transmitted to genital sites.
      - *C trachomatis* detected from an oropharyngeal specimen should be treated with azithromycin or doxycyline.
      - In populations with erratic health care–seeking behavior, poor compliance with treatment, or unpredictable follow-up, azithromycin may be more cost-effective because it offers single-dose, directly observed therapy.
  - Erythromycin.
    - Might be less efficacious than azithromycin and doxycycline, mainly because gastrointestinal side effects frequently discourage patients from compliance
  - Ofloxacin and levofloxacin.
    - Effective but more expensive
    - No advantage with regard to dose regimen
  - Other quinolones.
    - Not reliably effective against chlamydial infection *or*
    - Have not been adequately evaluated
  - To maximize adherence to recommended therapies, dispense medications for chlamydial infections on site; the first dose should be directly observed.

N gonorrhoeae

Dual Therapy for Gonococcal and Chlamydial Infection

- Patients infected with *N gonorrhoeae* often are coinfected with *C trachomatis.*
- Patients treated for gonococcal infection should be treated routinely with a regimen effective against uncomplicated genital *C trachomatis*.
- Most gonococci in the United States are susceptible to doxycycline and azithromycin; thus, routine co-treatment might hinder development of antimicrobial-resistant *N gonorrhoeae.*
- Limited data suggest that dual therapy with azithromycin might also enhance efficacy of oral cephalosporins if used to treat pharyngeal gonococcal infection.

Antimicrobial-Resistant N gonorrhoeae

- Treatment is complicated by the ability of this organism to develop resistance to antimicrobials.
- Quinolone-resistant strains are widespread through the United States and the world, and, as of 2007, this class is no longer recommended for gonococcal infection (and associated conditions, such as PID) in the United States.
- The proportion of isolates in the CDC Gonococcal Isolate Surveillance Project demonstrating decreased susceptibility to ceftriaxone or cefixime has remained very low.
- Most treatment failures from use of oral cephalosporins have been reported from Asian countries; hence, physicians should ask patients testing positive for gonorrhea about recent travel to and sexual activity in these countries.

Uncomplicated Gonococcal Infections of the Cervix, Urethra, and Rectum

- Recommended regimen.
  - Ceftriaxone 250 mg intramuscularly (IM) in a single dose *plus*
  - Azithromycin 1 g orally in a single dose
- Alternative regimens.
  - If ceftriaxone is not available
    - Cefixime 400 mg orally in a single dose *plus*
    - Azithromycin 1 g orally in single dose
- To maximize compliance, medications for gonococcal infections should be dispensed on site.
- Ceftriaxone in a single injection of 250 mg provides sustained, high bactericidal levels in the blood.
- Extensive clinical experience indicates that ceftriaxone is safe and effective for uncomplicated gonorrhea at all anatomic sites, curing 99.2% of uncomplicated urogenital and anorectal and 98.9% of pharyngeal infections.
- The 250-mg (rather than the 125-mg) dose of ceftriaxone is now recommended given
  - Increasingly wide geographic distribution of isolates demonstrating decreased susceptibility to cephalosporins in vitro
  - Reports of ceftriaxone treatment failures
  - Improved efficacy of ceftriaxone 250 mg to treat pharyngeal infection (which often goes unrecognized)
  - The utility of having a simple and consistent recommendation for treatment regardless of anatomic site
- The 400-mg oral dose of cefixime does not provide as high or as sustained a bactericidal level compared with the 250-mg dose of ceftriaxone.
  - In published clinical trials, the 400-mg dose cured 97.5% of uncomplicated urogenital and anorectal and 92.3% of pharyngeal gonococcal infections.
- Although cefixime can be given orally, this advantage is offset by the limited efficacy for treating pharyngeal gonococcal infection.
- Ongoing use of cefixime may hasten the development of resistance to ceftriaxone.
- The use of ceftriaxone in conjunction with azithromycin may potentially slow the emergence of resistance to cephalosporins.
- Single-dose cephalosporin regimens that are safe and highly effective against uncomplicated urogenital and anorectal gonococcal infections include
  - Ceftizoxime 500 mg IM
  - Cefoxitin 2 g IM with probenecid 1 g orally
  - Cefotaxime 500 mg IM
- None of the injectable cephalosporins offer any advantage over ceftriaxone for urogenital infection.

Uncomplicated Gonococcal Infections of the Pharynx

- Most are asymptomatic.
- More difficult to eradicate than infections at urogenital and anorectal sites.
- Few antimicrobial regimens, including those involving oral cephalosporins, can reliably cure >90% of gonococcal pharyngeal infections.
- Ask about oral sexual exposure; treat those reporting this with a regimen that has acceptable activity against pharyngeal infection.
- Although chlamydial coinfection of pharynx is unusual, coinfection at genital sites sometimes occurs.
  - Therefore, treatment for gonorrhea and chlamydia is suggested.
- Recommended regimen.
  - Ceftriaxone 250 mg IM in a single dose *plus*
  - Azithromycin 1 g orally in a single dose

DGI

- Hospitalization is recommended for initial therapy in patients
  - Who cannot be relied on to adhere to treatment
  - In whom the diagnosis is uncertain
  - With purulent synovial effusions or other complications
- Examine patients for clinical evidence of endocarditis and meningitis.
- For patients receiving therapy for DGI, presumptively treat for concurrent *C trachomatis* infection unless appropriate testing excludes it.
- Recommended regimen.
  - Ceftriaxone 1 g IM or intravenously (IV) every 24 hours *plus*
  - Azithromycin 1 g orally in a single dose
- Alternative regimens.
  - Cefotaxime 1 g IV every 8 hours *or*
  - Ceftizoxime 1 g IV every 8 hours *plus*
  - Azithromycin 1 g orally in a single dose
- Continue all regimens for 24–48 hours after improvement begins, at which time therapy may be switched to another oral agent guided by antimicrobial testing to complete at least 1 week of antimicrobial therapy.
- No treatment failures have been reported with the recommended regimens.

HPV (Genital Warts)

- The primary goal of treating visible genital warts is the removal of the warts.
- In most patients, treatment can induce wart-free periods.
- Left untreated, visible warts may resolve, may remain unchanged, or may increase in size or number.
- Available treatments likely reduce, but probably do not eradicate, HPV infectivity.
- Whether the reduction in HPV viral DNA resulting from treatment affects future transmission remains unclear.
- No evidence links the presence of genital warts or their treatment with the development of cervical cancer.
- Treatment of genital warts should be guided by
  - Patient preference
  - Available resources
  - Experience of primary care physician
- No definitive evidence suggests that any of the available treatments is superior to others.
- No single treatment is ideal for all patients or all warts.
- An acceptable alternative for some people is to forgo treatment and wait for spontaneous resolution.
- Factors that influence selection of treatment include
  - Wart size and number
  - Anatomic site of infection
  - Wart morphology
  - Patient preference
  - Cost of treatment
  - Convenience
  - Adverse effects
  - Physician experience
- In general, warts on moist surfaces or in intertriginous areas respond best to topical treatment.
- Change treatment method if patient has not improved substantially after a complete course of treatment or if side effects are severe.
- Most genital warts respond within 3 months of therapy.

Recommended Regimens for External Genital Warts

- Patient-applied options.
  - Imiquimod 3.75% or 5% cream
    - Patients should apply imiquimod cream once daily at bedtime, 3 times a week for up to 16 weeks.
    - Wash treatment area with mild soap and water 6–10 hours after application.
    - Safety during pregnancy has not been established, but animal data suggest that risk is low.
  - Podofilox 0.5% solution or gel
    - Patients should apply podofilox solution with a cotton swab, or podofilox gel with a finger, to visible genital warts twice a day for 3 days, followed by 4 days of no therapy.
    - Repeat cycle as necessary for a total of 4 cycles.
    - The total wart area treated should not exceed 10 cm, and total volume of podofilox should not exceed 0.5 mL per day.
    - If possible, the primary care physician should apply initial treatment to show proper technique and identify which warts should be treated.
    - Safety during pregnancy has not been established.
  - Sinecatechins 15% ointment
    - Apply 3 times daily (0.5 cm strand of ointment to each wart) using a finger to ensure complete coverage until complete clearance.
    - Do not continue for >16 weeks.
    - Do not wash off medication after application.
    - Avoid all sexual activity while the ointment is on the skin.
    - Not recommended for HIV-positive or immunocompromised individuals or for persons with genital herpes.
    - Safety during pregnancy is unknown.
- Physician-administered options.
  - Cryotherapy with liquid nitrogen or cryoprobe.
    - Repeat every 1–2 weeks.
    - Local anesthesia might facilitate treatment if warts are present in many areas or if area of warts is large *or*
  - Surgical removal by
    - Tangential scissor excision
    - Tangential shave excision
    - Curettage
    - Electrosurgery *or*
  - Trichloroacetic acid (TCA) or bichloroacetic acid (BCA) 80%–90%.
    - Apply a small amount only to warts and allow to dry (at which time a white frosting develops) before the patient sits or stands up.
    - If pain is intense, acid can be neutralized with soap or sodium bicarbonate.
    - Powder with talc, sodium bicarbonate (baking soda), or liquid soap to remove unreacted acid if an excess is applied.
    - Repeat weekly if necessary.

- Because of the shortcomings of available treatments, some physicians simultaneously use 2 or more modalities on the same wart.
  - Data are limited on efficacy or risks associated with such combinations.

- Alternative treatments include
  - Intralesional interferon *or*
  - Photodynamic therapy *or*
  - Topical cidofovir
- Recommended regimens for cervical warts include
  - Cryotherapy with liquid nitrogen *or*
  - Surgical removal *or*
  - TCA or BCA 80%–90% solution
- For women who have exophytic cervical warts, high-grade squamous intraepithelial lesions must be excluded before treatment is begun.
- Management of exophytic cervical warts should include consultation with a specialist.
- Recommended regimens for vaginal warts include
  - Cryotherapy with liquid nitrogen *or*
    - Use of a cryoprobe in the vagina is not recommended because of risk for perforation and fistula formation.
  - Surgical removal *or*
  - TCA or BCA 80%–90%
- Recommended regimens for urethral meatus warts include
  - Cryotherapy with liquid nitrogen *or*
  - Podophyllin 10%–25% in compound tincture of benzoin
    - Treatment area must be dry before contact with normal mucosa.
    - Can be applied weekly if necessary.
    - Safety during pregnancy has not been established.
    - Data on podofilox and imiquimod for treating distal meatal warts are limited.
- Recommended regimen for intra-anal warts include
  - Cryotherapy with liquid nitrogen *or*
  - Surgical removal *or*
  - TCA or BCA 80%–90%.
  - Manage intra-anal warts in consultation with a specialist.

HSV

- Genital HSV infection
  - Recommended regimens
    - Acyclovir 400 mg orally 3 times daily for 7–10 days *or*
    - Acyclovir 200 mg orally 5 times daily for 7–10 days *or*
    - Valacyclovir 1 g orally 2 times daily for 7–10 days *or*
    - Famciclovir 250 mg orally 3 times daily for 7–10 days.
    - Treatment may be extended if healing is incomplete after 10 days of therapy.
- Established HSV-2 infection
  - Most patients with symptomatic, first-episode genital HSV-2 infection will have recurrent episodes of genital lesions.
  - Recurrences are less frequent after initial genital HSV-1 infection.
  - Intermittent asymptomatic shedding occurs in persons with genital HSV-2 infection, even in those with longstanding or clinically silent infection.
  - Antiviral therapy for recurrent disease can be administered
    - Episodically to ameliorate or shorten the duration of lesions *or*
    - Continuously as suppressive therapy to reduce the frequency of recurrence
  - Many persons benefit from antiviral therapy; therefore, options for treatment should be discussed.
  - Some persons may prefer suppressive therapy, which has the advantage of decreasing risk of genital HSV-2 transmission to susceptible partners.
  - Daily suppressive therapy reduces the frequency of genital herpes recurrences by 70%–80% in patients who have frequent recurrences (ie, ≥6 per year).
  - Treatment is also effective in patients with less frequent recurrences.
  - Suppressive therapy (valacyclovir 500 mg daily) decreases HSV-2 transmission in discordant, heterosexual couples in which the source partner has a history of genital HSV-2 infection.
  - Suppressive therapy probably reduces transmission in persons with multiple partners (including men who have sex with men) and those who are HSV-2 seropositive without a history of genital herpes.
  - Recommended regimens include
    - Acyclovir 400 mg orally twice daily *or*
    - Valacyclovir 500 mg orally once daily *or*
    - Valacyclovir 1 g orally once daily *or*
    - Famciclovir 250 mg orally twice daily
  - Valacyclovir 500 mg once a day may be less effective than other valacyclovir or acyclovir regimens in patients with very frequent recurrences (≥10 episodes per year).

- Episodic therapy for recurrent genital herpes
  - Initiate within 1 day of lesion onset or during the prodrome that precedes some outbreaks.
  - Provide the patient with a supply of drug or prescription with instructions to initiate treatment as soon as symptoms begin.
  - Recommended regimens include
    - Acyclovir 400 mg orally 3 times daily for 5 days *or*
    - Acyclovir 800 mg orally twice daily for 5 days *or*
    - Acyclovir 800 mg orally 3 times daily for 2 days *or*
    - Valacyclovir 500 mg orally twice daily for 3 days *or*
    - Valacyclovir 1 g orally once daily for 5 days *or*
    - Famciclovir 125 mg orally twice daily for 5 days *or*
    - Famciclovir 1,000 mg orally twice daily for 1 day *or*
    - Famciclovir 500 mg orally once, followed by 250 mg twice daily for 2 days

M genitalium

- 7-day doxycycline treatment regimen for urethritis is largely ineffective to treat *M genitalium*.
- 1 g orally of azithromycin is effective, but resistance is rapidly emerging.
  - Longer course of azithromycin (500 mg on day 1, followed by 250 mg daily for 4 days) may be marginally more effective.
  - People in whom the 1-g course fails generally do not respond to a longer course.
- Moxifloxacin (400 mg daily for 7, 10, or 14 days) has been successfully used to treat men and women with previous treatment failures, but the drug has not been tested in clinical trials.

Primary and Secondary Syphilis

- Parenteral penicillin G is the preferred drug for treating all stages of syphilis.
  - Preparation or preparations used (ie, benzathine, aqueous procaine, aqueous crystalline), dose, and length of treatment all depend on stage and clinical manifestations.
  - Recommended regimen for children.
    - Evaluate children with acquired primary or secondary syphilis for sexual abuse (including consultation with child protective services) and treat with the following regimen:
      - Benzathine penicillin G 50,000 units/kg IM, up to adult dose of 2.4 million units in a single dose.
      - A child or adolescent weighing ≥48 kg would receive the adult dose.
- Latent syphilis.
  - Not transmitted sexually; thus, the objective of treatment is to prevent late complications.
  - Although clinical experience supports effectiveness of penicillin, limited evidence is available for specific regimens.
  - Recommended regimen for adults (penicillin-nonallergic patients who have normal CSF examination, if performed).
    - Early latent syphilis
      - Benzathine penicillin G 2.4 million units IM in a single dose
        - Recommended also for HIV-infected patients
    - Late latent syphilis or latent syphilis of unknown duration
      - Benzathine penicillin G 7.2 million units total, administered as 3 doses of 2.4 million units IM each at 1-week intervals
        - Recommended also for HIV-infected patients
  - Recommended regimens for children.
    - Treat older children with acquired latent syphilis using the following pediatric regimens:
    - These regimens are for penicillin-nonallergic children with acquired syphilis who have normal CSF examination results.
    - Early latent syphilis.
      - Benzathine penicillin G 50,000 units/kg IM, up to adult dose of 2.4 million units, in a single dose (A child or adolescent who weighs ≥48 kg would receive the adult dose.)
    - Late latent syphilis or latent syphilis of unknown duration.
      - Benzathine penicillin G 50,000 units/kg IM, up to adult dose of 2.4 million units, administered as 3 doses at 1-week intervals (total 150,000 units/kg up to the adult dose of 7.2 million units)

PID

- When selecting a treatment regimen, consider availability, cost, patient acceptance, and antimicrobial susceptibility.

- Evidence is insufficient to recommend removal of an intrauterine device in women diagnosed with PID.
- Comprehensive observational and controlled studies demonstrate that HIV-infected women with PID have similar symptoms compared with uninfected controls.
  - Except were more likely to have a tubo-ovarian abscess.
  - Both groups responded equally well to standard parenteral and oral antibiotic regimens.
  - Whether or not immunodeficient HIV-infected women with PID require more aggressive treatment is uncertain.
- Parenteral treatment.
  - For mild to moderate PID, parenteral therapy and oral therapy seem to have similar efficacy.
  - Clinical experience should guide transition to oral therapy, which usually can begin within 24–48 hours of clinical improvement.
  - At least 24 hours of direct inpatient observation is recommended for patients who have tubo-ovarian abscess.
  - Recommended parenteral regimens include
    - Cefotetan 2 g IV every 12 hours *plus*
    - Doxycycline 100 mg orally or IV every 12 hours *or*
    - Cefoxitin 2 g IV every 6 hours *plus*
    - Doxycycline 100 mg orally or IV every 12 hours *or*
    - Clindamycin 900 mg IV every 8 hours *plus*
    - Gentamicin loading dose IV or IM (2 mg/kg) followed by a maintenance dose (1.5 mg/kg) every 8 hours; single daily dosing (3–5 mg/kg) can be substituted.
    - Other considerations include
      - Doxycycline should be administered orally when possible, even when patient is hospitalized.
      - Although use of a single daily dose of gentamicin has not been evaluated for PID, it is efficacious in analogous situations.
      - Discontinue parenteral therapy 24–48 hours after clinical improvement.
      - Oral therapy with doxycycline (100 mg twice a day) should continue for a total of 14 days.
      - For tubo-ovarian abscess, clindamycin or metronidazole with doxycycline can be used for continued therapy rather than doxycycline alone.
        - Provides more effective anaerobic coverage
    - Other second- or third-generation cephalosporins (eg, ceftizoxime, cefotaxime, ceftriaxone) might be effective therapy and might replace cefotetan or cefoxitin.
      - However, they are less active than cefotetan or cefoxitin against anaerobic bacteria.
  - Other considerations include
    - Discontinue parenteral therapy 24 hours after clinical improvement.
    - Continuing oral therapy should consist of doxycycline 100 mg orally twice daily or clindamycin 450 mg orally 4 times daily to complete a total of 14 days of therapy.
    - For tubo-ovarian abscess, clindamycin should be continued rather than doxycycline for more effective anaerobic coverage.
  - Alternative parenteral regimens include
    - Ampicillin/sulbactam 3 g IV every 6 hours *plus*
    - Doxycycline 100 mg orally or IV every 12 hours.
    - Ampicillin/sulbactam plus doxycycline is effective against *C trachomatis*, *N gonorrhoeae*, and anaerobes in women with tubo-ovarian abscess.
    - One trial demonstrated high short-term clinical cure rates with azithromycin, either as monotherapy for 1 week (500 mg IV for 1 or 2 doses followed by 250 mg orally for 5–6 days) or combined with a 12-day course of metronidazole.
- Intramuscular/oral treatment.
  - Can be considered for mild to moderately severe acute PID, given that clinical outcomes are similar to those of women treated with parenteral therapy.
  - Patients who do not respond to IM or oral therapy within 72 hours should be reevaluated to confirm diagnosis and should be administered parenteral therapy.
  - Recommended oral regimen.
    - Ceftriaxone 250 mg IM in a single dose *plus*
    - Doxycycline 100 mg orally twice daily for 14 days, *with or without*
    - Metronidazole 500 mg orally twice daily for 14 days *or*
    - Cefoxitin 2 g IM in a single dose and probenecid 1 g orally administered concurrently in a single dose *plus*
    - Doxycycline 100 mg orally twice daily for 14 days, *with or without*

- Metronidazole 500 mg orally twice daily for 14 days *or*
- Other parenteral third-generation cephalosporin (eg, ceftizoxime, cefotaxime) *plus*
- Doxycycline 100 mg orally twice daily for 14 days, *with or without*
- Metronidazole 500 mg orally twice daily for 14 days

- Other considerations include
  - Recommended third-generation cephalosporins are limited in anaerobic coverage.
    - Therefore, until it is known that extended anaerobic coverage is not important for acute PID, the addition of metronidazole should be considered.
  - These regimens provide coverage against frequent etiologic agents of PID, but the optimal choice of cephalosporin is unclear.
  - Cefoxitin has better anaerobic coverage than ceftriaxone and, in combination with probenecid and doxycycline, has been effective in short-term clinical response.
  - Ceftriaxone has better coverage against *N gonorrhoeae.*
  - Metronidazole will also effectively treat bacterial vaginosis, often associated with PID.

- Alternative oral regimens.
  - Azithromycin has shown short-term effectiveness in at least one clinical trial (500 mg IV daily for 1–2 doses, followed by 250 mg orally daily for 12–14 days) or in combination with metronidazole.
  - In another study, it was effective when 1 g orally once per week for 2 weeks was used in combination with ceftriaxone 250 mg IM in a single dose.
  - Concomitant use of metronidazole for anaerobic coverage should be considered.
  - As a result of the emergence of quinolone-resistant *N gonorrhoeae,* regimens that include a quinolone agent are no longer recommended.
  - If parenteral cephalosporin therapy is not feasible, community prevalence and individual risk for gonorrhea are low, and follow-up is likely, use fluoroquinolones.
    - Levofloxacin 500 mg orally once daily *or*
    - Ofloxacin 400 mg orally twice daily for 14 days *or*
    - Moxifloxacin 400 mg orally once daily for 14 days, *with*
    - Metronidazole 500 mg orally twice daily for 14 days
  - Perform tests for gonorrhea before instituting therapy.
  - Manage as follows if the test result is positive:
    - Base treatment on results of antimicrobial susceptibility.
    - If the isolate is determined to be quinolone-resistant *N gonorrhoeae,* or antimicrobial susceptibility cannot be assessed (if only NAAT is available), consultation with an infectious disease specialist is recommended.

Perihepatitis (Fitz-Hugh–Curtis Syndrome)

- Treatment for PID eliminates perihepatitis.

Epididymitis

- Empiric therapy is indicated before laboratory test results are available.
- All patients should receive ceftriaxone plus doxycycline for initial treatment.
- Additional therapy may include a quinolone if
  - Acute epididymitis is not caused by gonorrhea (results of NAAT are negative) *or*
  - Infection is most likely caused by enteric organisms.
  - For men who are at risk for sexually transmitted and enteric organisms (eg, men who report anal insertive intercourse), ceftriaxone and a fluoroquinolone are recommended.
- Recommended regimens.
  - For acute epididymitis most likely caused by sexually transmitted chlamydia and gonorrhea
    - Ceftriaxone 250 mg IM in single dose *plus*
    - Doxycycline 100 mg orally twice daily for 10 days
  - For acute epididymitis most likely caused by sexually transmitted chlamydia and gonorrhea and enteric organisms (eg, in men who practice insertive anal sex)
    - Ceftriaxone 250 mg IM in a single dose *plus*
    - Levofloxacin 500 mg orally once daily for 10 days *or*
    - Ofloxacin 300 mg orally twice daily for 10 days
  - For acute epididymitis most likely caused by enteric organisms
    - Levofloxacin 500 mg orally once daily for 10 days *or*
    - Ofloxacin 300 mg orally twice daily for 10 days

Proctitis, Proctocolitis, and Enteritis

- Recommended regimen.
  - Ceftriaxone 250 mg IM *plus*
  - Doxycycline 100 mg orally twice daily for 7 days
- Bloody discharge, perianal ulcers, or mucosal ulcers among patients with acute proctitis and either a positive rectal chlamydia NAAT or HIV infection should be offered presumptive treatment for LGV (doxycycline 100 mg orally twice daily for 3 weeks).
- Patients with suspected or documented herpes proctitis should be managed as for genital herpes.

Vaginitis

- Treatment is warranted for
  - Symptomatic women who have bacterial vaginosis
  - Asymptomatic women scheduled to undergo abortion or hysterectomy

Cervicitis

- Presumptively treat the following women for *C trachomatis*, especially if follow-up is uncertain or if NAAT is unavailable:
  - Who have cervicitis and are ≤25 years
  - Who engage in unprotected sex
  - Who have a new sex partner, a sex partner with concurrent partners, or a sex partner with an STI
- Appropriate therapy for gonorrhea should be provided if prevalence of infection in patient population is >5%.

Urethritis

- Adolescents with recurrent and persistent urethritis should first be evaluated to make certain that they completed a full treatment course and were not reinfected.
- The most common cause of recurrent or persistent nongonococcal urethritis is *M genitalium*.
- Men initially treated with doxycycline should be treated with 1 g of azithromycin.
- Those who fail a regimen of azithromycin should be treated with moxifloxacin 400 mg orally for 7 days.
- *T vaginalis* can cause urethritis.
- In areas where *T vaginalis* is prevalent, men who have sex with women should be treated with metronidazole 2 g orally in a single dose or tinidazole 2 g orally in a single dose.

WHEN TO ADMIT

- PID[4]
  - In mild or moderate PID, outpatient therapy yields short- and long-term clinical outcomes similar to inpatient therapy.
  - The decision to hospitalize should be based on the judgment of the primary care physician and the following criteria:
    - Surgical emergencies, such as appendicitis, cannot be excluded.
    - The patient is pregnant.
    - The patient does not respond clinically to oral antimicrobial therapy.
    - The patient cannot follow or tolerate an outpatient oral regimen.
    - The patient has severe illness, nausea and vomiting, or high fever.
    - The patient has a tubo-ovarian abscess.
  - No evidence suggests that adolescents benefit from hospitalization for PID.
    - The decision should be based on the same criteria used for older women.
    - Younger women with mild to moderate acute PID have similar outcomes with outpatient or inpatient therapy.
    - Clinical response to outpatient therapy is similar among adolescents and older women.
  - At least 24 hours of direct inpatient observation is recommended for patients who have tubo-ovarian abscesses.
- Epididymitis
  - Consider hospitalization if
    - Pain is particularly severe.
    - Patient is febrile.
    - Nonadherence is a concern.

WHEN TO REFER

- If the physician is inexperienced in the diagnosis or management of
  - PID
  - DGI
  - Syphilis (or positive VDRL or RPR test)
  - Anogenital warts
  - Genital herpes
  - Abnormal Papanicolaou (Pap) tests
  - Recurrent or persistent urethritis
  - Proctitis, proctocolitis
- If postexposure prophylaxis for HIV infection is being considered in the management of a sexual assault victim.

- In the case of sexual assault, survivors should be referred to a rape crisis center for evaluation and treatment if one is available.
- PID.
  - Depending on the experience of the physician, consider consultation with a gynecologist if abscess is detected or if patient fails to improve.
  - Consult with a surgeon if appendicitis is a possibility.

FOLLOW-UP

Specific Agents

- *C trachomatis*
  - Except for pregnant women, patients do not need to be retested after completing treatment unless
    - Adherence is in question.
    - Symptoms persist.
    - Reinfection is suspected.
  - False-negative results might occur because of small numbers of chlamydial organisms.
    - NAATs done <3 weeks after completion of therapy for patients treated successfully might yield false-positive results.
    - Rates of infection are high among women retested several months after treatment (presumably because of reinfection by an untreated or new sex partner).
    - Repeat infections confer increased risk for PID and other complications.
    - Chlamydia-infected men and women should be retested ~3 months after treatment, regardless of whether they think their sex partners have been treated.
    - If retesting at 3 months is not possible, retest when they next seek medical care within 3–12 months after the initial treatment.
- *N gonorrhoeae*
  - Test of cure is not indicated for uncomplicated gonorrhea treated with any recommended or alternative regimens.
  - Patients with symptoms that persist after treatment should be evaluated with culture for *N gonorrhoeae;* isolated gonococci should be tested for antimicrobial susceptibility.
  - Persistent urethritis, cervicitis, or proctitis also might be caused by *C trachomatis* or other organisms.
  - *N gonorrhoeae* infection is prevalent in patients diagnosed and treated for gonorrhea in the preceding several months.
    - Most are caused by reinfection, and not treatment failure.
  - Advise all patients with gonorrhea to be retested ≤3 months after treatment.
  - Those not seeking retesting ≤3 months should be tested when they next seek medical care in the ensuing 12 months.
- HPV
  - Careful follow-up is essential to monitor results and prevent regrowth.
  - The benefit of treating subclinical HPV infection in the absence of cervical dysplasia is unclear.
  - Examination and treatment of sex partners is of uncertain benefit.
  - Treatment modality should be changed if the patient has not improved substantially.
  - Most genital warts respond after ≤3 months of therapy.
  - Response and side effects should be evaluated throughout therapy.
- HSV
  - Lesions generally heal without scarring.
  - Safety and efficacy have been documented among patients receiving daily therapy with
    - Acyclovir for as long as 6 years
    - Valacyclovir or famciclovir for 1 year
  - Frequency of recurrence diminishes over time in many, and the patient's psychological adjustment to disease might change.
  - Periodically (eg, once a year), clinicians should discuss the need to continue suppressive therapy with the patient.

STIs/Syndromes Associated With STIs

- PID
  - If outpatient therapy is attempted, ensure careful follow-up at 48 hours and establish a mechanism for earlier hospitalization if symptoms worsen.
  - Patients should demonstrate substantial clinical improvement ≤72 hours of initiation of therapy.
    - Defervescence
    - Reduction in direct or rebound abdominal tenderness
    - Reduction in uterine, adnexal, and cervical motion tenderness
  - Patients who do not improve ≤72 hours usually require hospitalization, additional diagnostic tests, and surgical intervention.

- Assessment of the antimicrobial regimen and diagnostics (including the consideration of diagnostic laparoscopy for alternative diagnoses) is recommended in women without clinical improvement.
- Women with documented gonococcal or chlamydial infections have high rates of reinfection within 6 months of treatment.
- Repeat testing of these women is recommended 3–6 months after treatment, regardless of whether their sex partners were treated.
- All women with acute PID should be offered HIV testing.
- Male sex partners of women with PID should be examined and treated for gonorrhea and chlamydia if they had sexual contact with the patient during the 60 days preceding onset of symptoms.
- If the patient's last sexual intercourse was >60 days before onset of symptoms or diagnosis, the most recent partner should be treated.

■ Primary and secondary syphilis
- Treatment failure can occur with any regimen.
- Assessing response is often difficult; no definitive criteria for cure or failure have been established.
- Nontreponemal test titers may decline more slowly for patients who previously had syphilis.
- Patients should be reexamined clinically and serologically 6 and 12 months after treatment; more frequent evaluation may be prudent if follow-up is uncertain.
- HIV-infected patients should be evaluated clinically and serologically for treatment failure at 3, 6, 9, 12, and 24 months after therapy.
- Patients with treatment failure or who are reinfected should be retreated and reevaluated for HIV infection if
  - Signs or symptoms persist or recur.
  - They have a sustained 4-fold increase in nontreponemal test titer (ie, compared with the maximum or baseline titer at time of treatment).
- Treatment failure usually cannot be reliably distinguished from reinfection with *T pallidum;* lumbar puncture should be performed.
- HIV-infected patients who meet the criteria for treatment failure should be managed in the same manner as HIV-negative patients with CSF examination and retreatment as indicated as follows.
- Failure of nontreponemal test titers to decline 4-fold within 6 months after therapy for primary or secondary syphilis might indicate probable treatment failure.
- Persons whose titers remain serofast should be reevaluated for HIV infection.
  - Optimal management is unclear.
  - At a minimum, patients should have additional clinical and serologic follow-up.
  - If follow-up cannot be ensured, retreatment is recommended.
- Because treatment failure might be the result of unrecognized central nervous system infection, many specialists recommend CSF examination.
- When patients are retreated, most experts recommend
  - Weekly injections of benzathine penicillin G 2.4 million units IM for 3 weeks *unless*
  - CSF examination indicates that neurosyphilis is present.

■ Latent syphilis
- Patients who are seroreactive but do not have any physical findings of infection are classified as having latent syphilis.
- Patients who are known to have seroconverted within the previous 12 months are classified as having early latent syphilis, as are those who, within the previous year
  - Have had unequivocal symptoms of primary or secondary syphilis
  - Have had a sex partner documented to have primary, secondary, or early latent syphilis
  - Have reactive treponemal and nontreponemal tests with the only possible exposure occurring within the previous year
- Absent these conditions, an asymptomatic person is considered to have late latent syphilis or syphilis of unknown duration.
- Repeat quantitative nontreponemal serologic tests at 6, 12, and 24 months.
- A CSF examination should be performed if
  - Titers increase 4-fold.
  - An initially high titer (≥1:32) fails to decrease at least 4-fold (ie, 2 dilutions) within 12–24 months.
  - Signs or symptoms attributable to syphilis develop.
- In such circumstances, even if CSF examination result is negative, retreatment for latent syphilis should be initiated.

- HIV-infected patients should be evaluated clinically and serologically at 6, 12, 18, and 24 months after therapy.
- If clinical symptoms develop or nontreponemal test titers rise 4-fold, CSF examination should be performed and treatment administered accordingly.

- Epididymitis
  - Adolescents treated as outpatients should be followed up with within 48–72 hours of initiating treatment.
  - Failure to improve should prompt reevaluation of diagnosis and treatment.
  - Sex partners of adolescents with epididymitis suspected or confirmed to be caused by chlamydia or gonorrhea should be evaluated and treated if their contact with index patient occurred <60 days before onset of the patient's symptoms.
- Cervicitis
  - A follow-up visit should be scheduled to determine if the cervicitis has resolved.
  - Women with persistent or recurrent cervicitis despite appropriate treatment should be evaluated for reexposure or treatment failure.
  - Management options for persistent cervicitis are undefined and whether repeat or prolonged antibiotic regimens are effective is unknown.

Sexual Assault

- As follow-up with sexual assault victims is often suboptimal, preventive therapy for STIs should be encouraged.
  - Empiric treatment for chlamydia, gonorrhea, and trichomonas
    - Ceftriaxone 250 mg IM *plus* azithromycin 1 g orally in a single dose *plus* metronidazole 2 g orally in a single dose *or* tinidazole 2 g orally in a single dose
  - HPV vaccination for those who have not received any doses or have failed to complete the series
  - Hepatitis B vaccination with or without hepatitis B immunoglobulin depending on vaccination status and the hepatitis B surface antigen status of the assailant, if known
- Emergency contraception should be offered.
- Although frequency is low, HIV seroconversion has occurred in individuals in whom the only identified risk factor was sexual assault.
  - Risk for transmission influenced by
    - Nature of the assault
    - Infection status of the perpetrator
    - Genital lesions and STIs (clinically apparent or asymptomatic) in the victim
- If postexposure prophylaxis to prevent HIV infection is being considered, consultation with an HIV specialist is recommended.
- Follow-up in 2–3 months is recommended to
  - Detect repeat or new infections.
  - Monitor serostatus of the victim if HIV, hepatitis B infection, or syphilis is a concern.

COMPLICATIONS

- Long-term sequelae of STIs.
  - Cervical cancer
  - Infertility
  - Ectopic pregnancy
  - Chronic pelvic pain
  - AIDS
- Individuals infected with ≥1 STIs are more likely than those without to acquire HIV infection and transmit to an uninfected partner.
  - STIs may cause breakdown of the genital mucosa (providing a portal of entry for HIV) and recruit CD4 cells to the area of infection.
  - STI acquisition may be a marker for unmeasured behavioral characteristics that contribute to the observed link.
  - Current evidence indicates that the effect of STI treatment on HIV incidence rates varies as a function of sexual behaviors and STI prevalence of the target population.
- Specific agents.
  - *C trachomatis*
    - Infection with chlamydia is not an independent risk factor for cervical dysplasia, but it may play some role.
    - An untreated infected woman can pass the organism to her newborn through colonization during birth.
  - *N gonorrhoeae*
    - Gonorrhea may produce epididymitis and PID.
    - In contrast with chlamydia, the gonococcal organism can become blood-borne and lead to so-called arthritis-dermatitis syndrome or DGI.
  - HPV
    - Associated with >90% of cervical dysplasia worldwide.
    - Complications rarely occur if wart treatments are used properly.

- Persistent hypopigmentation or hyperpigmentation is common with ablative modalities.
- Depressed or hypertrophic scars are rare but can occur, especially if the patient has had insufficient time to heal between treatments.
- Treatment can result, rarely, in disabling chronic pain syndromes (eg, vulvodynia or analdynia, hyperesthesia of the treatment site) or painful defecation or anal fistulas.
- A limited number of case reports of severe systemic effects from podophyllin resin and interferon have been documented.
- Mild to moderate pain or local irritation might develop after treatment with podofilox.
- Sinecatechins (a botanical drug).
  - Side effects include erythema, pruritus, burning, pain, ulceration, edema, induration, and vesicular rash.
  - May weaken condoms and diaphragms.

- HSV
  - HSV infections of the male and female genital tract are distressing because of the potential for recurrence, especially if caused by HSV-2.
  - After infection resolves, virus remains latent in the sacral ganglia and may reactivate at any time.
  - Vesicles usually occur near initial site but tend to be fewer in number.
  - Just before recurrence, the patient may experience burning or itching at the site of infection.
  - Healing takes 1–2 weeks.
  - Recurrences may be associated with stress, local trauma, fever, or menstruation and tend to be shorter and less symptomatic.
  - Asymptomatic genital shedding of HSV-2 occurred on 26% of days in the first year after initial episode, 13% of days in years 1–9, and 9% of days after ≥10 years.
  - In the year after a first documented episode of genital HSV-2 infection, 90% will have ≥1 recurrences, about one-third will have ≥6, and one-fifth will have ≥10.
  - The risk of recurrence depends on many factors and is greater in
    - Male adolescents
    - Those whose infection was caused by HSV-2
    - Those who experience a second episode
  - Some patients with recurrent disease benefit from therapy if it begins during prodrome or within 1 day of lesion onset.
  - Those with ≥6 recurrences per year have a 75% reduction in recurrences with daily suppressive therapy.
  - Patient-initiated administration of a single-day course of famciclovir also shortens the duration of recurrences.
  - Valacyclovir reduces asymptomatic virus shedding and reduces risk of infection in couples who are serodiscordant for HSV-2.

- STIs/syndromes associated with STIs.
  - PID
    - In the short term, PID can lead to such problems as a tubo-ovarian abscess.
    - In the long run, the following conditions are attributable to PID, even when an acute episode has been managed appropriately:
      - Tubal factor infertility
      - Chronic pelvic pain
      - Increased risk for ectopic pregnancy
    - ~10%–20% of patients with PID develop a tubo-ovarian abscess; 3%–15% of these abscesses rupture.
  - Syphilis
    - Patients with syphilis who demonstrate any of the following conditions should have a prompt CSF examination:
      - Neurologic (eg, auditory disease, cranial nerve dysfunction, acute or chronic meningitis, stroke, changes in mental status, loss of vibration sense) or ophthalmic signs or symptoms (iritis or uveitis)
      - Evidence of active tertiary syphilis (eg, aortitis, gumma)
      - Treatment failure
    - If a patient misses a dose of penicillin in a course of weekly therapy for late syphilis, the appropriate course is unclear.
      - If the interval between doses is 10–14 days, restarting injections may not be necessary.

PREVENTION

- Specific agents
  - *C trachomatis*
    - Screening programs reduce the incidence of PID.

- Treatment of infected patients prevents transmission to sex partners.
  - Treatment of sex partners helps prevent reinfection of the index patient and infection of other partners.
  - Instruct patients treated for chlamydia to abstain from sexual intercourse for 7 days after single-dose therapy or until completion of a 7-day regimen.
  - Instruct patients to abstain from sexual intercourse until all sex partners are treated to minimize the risk for reinfection.
- For infected pregnant women, treatment usually prevents transmission to neonates during birth.

• HPV
- Comprehensive cervical cytology screening program with Pap test to detect premalignant changes in the cervix (cervical intraepithelial neoplasia, usually caused by HPV infection) is a cornerstone of cervical cancer prevention efforts in the United States.
  - However, the natural history of cervical intraepithelial neoplasia is not well understood, and HPV infection generally is self-limited.
  - Pap test screening in adolescents can lead to unnecessary and expensive diagnostic testing that may be associated with psychologic and physiologic morbidity.
  - American Congress of Obstetricians and Gynecologists recommends that Pap test screening begin at age 21 years, regardless of the age of first intercourse.
    - This recommendation does not apply to women who have HIV infection, are immunosuppressed, or have had a previous diagnosis of cervical intraepithelial neoplasia or cancer.
- HPV DNA testing.
  - Not indicated in women <21 years.
  - May be used in the management of women ≥21 years with a diagnosis of atypical squamous cells of undetermined origin on Pap test, but repeating Pap test in 1 year is preferable.
- HPV vaccine.
  - 3 HPV vaccines have been licensed for use in the United States for prevention of cervical cancer.
    - Quadrivalent (HPV4) vaccine containing viruslike particles prepared from the recombinant L1 capsid proteins from HPV types 6, 11, 16, and 18
    - Bivalent (HPV2) vaccine containing viruslike particles prepared from the recombinant L1 capsid proteins from HPV types 16 and 18
    - 9-valent (HPV9) vaccine offering protection against HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58
  - Advisory Committee on Immunization Practices (ACIP) recommends routine vaccination of girls aged 11 or 12 years with 3 doses of HPV2, HPV4, or HPV9, but the series can be started beginning at age 9 years.
  - Schedule for both vaccines is the same.
    - Second dose should be administered 1–2 months after the first.
    - Third dose is administered 6 months after the first.
  - Minimum intervals between doses are as follows:
    - 4 weeks between the first and second doses
    - 12 weeks between the second and third doses
    - 24 weeks between the first and third doses
  - Doses administered at time intervals shorter than what is recommended should be repeated.
  - Vaccination with any of the 3 vaccines is also recommended for adolescent and young adult women aged 13–26 years who have not been vaccinated previously or have not received all 3 doses.
  - Women who turn 26 before completing the series can receive the additional doses.
  - The ACIP recommends the HPV2, HPV4, and HPV9 vaccines for the prevention of genital warts.
  - Vaccination in males.
    - The US Food and Drug Administration (FDA) also licensed the use of the HPV4 and HPV9 vaccines in boys aged 9–16 years.

- ▶ Vaccination of boys with HPV4 or HPV9 vaccine is recommended for those aged 13–21 years who have not previously been vaccinated or have not received all 3 doses; men aged 22–26 years may be vaccinated.
- ▶ HPV vaccination (HPV4 or HPV9) is recommended through age 26 years for men who have sex with men and for individuals with HIV or other immunocompromising conditions.
- ▶ Recent data demonstrate that the HPV4 vaccine prevents infection with HPV types 6, 11, 16, and 18 and related external genital lesions in men 16–26 years old.
- ▶ The FDA approved the use of the HPV4 and HPV9 vaccines for prevention of anal cancers and associated precancerous lesions caused by the HPV types included in the HPV4 and HPV9 vaccines in male and female adolescents and young adults 9–26 years old.

- Herpes genitalis
  - — A successful HSV vaccine has been elusive.

■ STIs/syndromes associated with STIs
- PID
  - — Because an episode of PID is a major risk factor for development of a second episode, the use of barrier methods of contraception must be stressed.
- Syphilis
  - — Most adolescents with syphilis will be identified only through routine serologic screening.
  - — Testing at-risk youth is important.

■ Clinicians should strongly consider screening any sexually active adolescent with a generalized eruption (eg, that seen with pityriasis rosea) for syphilis.

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DEFINITION

- The accepted medical definition of when a child is too short may be at variance with the point at which parents worry about their child's growth.
- The reference range for height encompasses 2 standard deviations (SDs) above and below the mean (between the 97th and 3rd percentiles).
  - The third percentile may be difficult to appreciate because the lowest curve on many growth charts is the fifth percentile.
- A single point on a growth chart often does not define a worrisome growth pattern.
  - Previous growth data should be plotted whenever available.
  - Any suggestion of growth deceleration should be reviewed.
- Standard growth charts do not incorporate pubertal stage.
  - Short children who start puberty relatively late may seem to fall further behind even though they are growing at a typical rate.

HISTORY

- The growth curve is most helpful for evaluation.
  - If the growth rate has been typical for the previous ≥2 years, the child most likely has constitutional growth delay (CGD) or familial short stature (FSS) and is unlikely to have a defined, treatable cause.
  - A single point that falls off the established curve is often a measurement error and should be rechecked.
- A history of stimulant medications or glucocorticoid use might be key information.
- Decreased energy level and poor appetite.
  - Could indicate a chronic, growth-limiting illness.
  - Many short, healthy children are picky eaters.
- Abnormal stool history could indicate
  - Malabsorption
  - Celiac disease
  - Inflammatory bowel disease
- Family history.
  - May suggest FSS in a healthy child who is short but growing at normal rate.
    - Height of parents and grandparents
    - Growth percentiles of siblings
  - Two-thirds of children with CGD have a family history of a parent who was a late maturer.
    - Mother's menarche after age 14
    - Father who continued to grow after high school

PHYSICAL EXAMINATION

- Usually, there are no physical findings that point to a specific diagnosis.
- In children with decreased subcutaneous fat stores, weight is more affected than height.
  - May not be getting enough calories
  - May have bowel disease or another chronic illness
- A short child who is relatively pudgy (particularly if excess rippled fat is present over the trunk) may have growth hormone (GH) deficiency.
- Dysmorphic features may suggest a syndrome associated with short stature.
  - In girls, look for Turner syndrome.
    - High-arched palate
    - Cubitus valgus
    - Fingernails that bend upward
- An enlarged thyroid may be the only clue to hypothyroidism.
- Pubertal staging should be done on any short child ≥10 years.
  - A short, healthy 14-year-old boy (and, less often, a short, healthy 13-year-old girl) who is still prepubertal is most likely to have CGD.
  - An adolescent with a flattened growth curve at 13–16 years and who is in the late stages of puberty has completed or has nearly completed growing (nothing can increase the individual's adult height).

DIFFERENTIAL DIAGNOSIS

- Most common causes of short stature
  - CGD
  - FSS
- Syndromes with short stature
  - Often associated with being born small for gestational age (SGA)
  - Turner syndrome
    - Should be considered in any girl with height well below the third percentile
    - Common features
      - Lymphedema as a newborn
      - Frequent ear infections >2 years
      - Narrow, high-arched palate
      - Cubitus valgus
      - Upturned fingernails
      - Webbed neck present in only ~40%
      - Congenital heart disease in ~15%
        - Coarctation of the aorta and bicuspid aortic valve are the most common.

- Silver-Russell syndrome
  - SGA
  - Triangular face with down-turned mouth
- Noonan syndrome
  - Typical facial features
    - Flat nasal bridge
    - Hypertelorism
    - Ptosis
  - Webbed neck
  - Cryptorchidism
  - Pulmonic stenosis
- Other syndromes with short stature
  - De Lange
  - Rubinstein-Taybi
  - Seckel

- Chronic illnesses and nutritional disorders
  - Should be considered in short children whose weight is further below the curve than their height or whose body mass index is <10% for age
  - Inadequate caloric intake
    - Not commonly the result of poverty in the United States because high-calorie foods are cheap
    - Overly restricted diet to avoid gaining weight or to lower cholesterol
      - Anorexia nervosa is the extreme example.
  - Inflammatory bowel disease
    - Growth attenuation may start before gastrointestinal (GI) symptoms are apparent.
  - Celiac disease
    - May have few, if any, GI symptoms
  - Renal disease
    - Renal tubular acidosis
    - Chronic renal failure
  - Liver disease
- Medication-related poor growth
  - Long-term oral glucocorticoid therapy
    - Much less effect from inhaled corticosteroids for asthma
  - Stimulant medications
- Endocrine disorders
  - Height is often more affected than weight.
  - GH deficiency.
    - Not a common cause of short stature.
    - Should be suspected in children below the third percentile who are falling further behind over time.
    - A suggestive physical finding is an increase in truncal subcutaneous fat.
    - Most cases are congenital, with falloff in growth starting late in the first or second year of life.
    - Acquired GH deficiency is less common and raises the possibility of a pituitary tumor.
    - Partial GH deficiency is difficult to distinguish from CGD and FSS.
  - Hypothyroidism.
    - Acquired hypothyroidism needs to be excluded in any child with growth deceleration, even if height is above the third percentile.
  - Cushing syndrome.
    - Endogenous Cushing syndrome is extremely rare.
    - Iatrogenic Cushing syndrome is more common.
    - Key findings include
      - Rapid truncal, rather than generalized, weight gain
      - Slowing of linear growth
      - Moon facies
      - Abdominal striae
      - Increased skin pigmentation
- Idiopathic short stature (ISS)
  - Moderately to severely short children who do not meet the criteria for CGD and FSS, often with subnormal rate of growth.
  - After extensive testing, no cause for poor growth is found.

LABORATORY EVALUATION

- Resist the temptation to order multiple laboratory tests for a child who is only mildly short (≥third percentile) and whose growth rate seems to be normal.
  - Clinically significant abnormal test results are rarely found to explain short stature.
- Screening tests before a visit with a specialist might be appropriate if
  - Height is well below third percentile.
  - Growth deceleration that cannot be explained by medication is well documented.
- A specialist can order any needed test at first consultation.
- Insulin-like growth factor 1 (IGF-1) is the best screening test if GH deficiency is suspected.
  - However, many children with CGD have borderline low IGF-1 levels for their age.
  - A random GH level is of no value because of the pulsatile nature of GH secretion.

- Thyroid testing.
  - Limit to free thyroxine (T_4) and thyroid-stimulating hormone (TSH).
    - Will identify primary and secondary hypothyroidism
  - Borderline TSH (5.5- to 10-mcU/mL range) with normal free T_4 is usually a normal variation and will not explain poor growth.
- Complete blood cell count and erythrocyte sedimentation rate are mainly useful in the occasional child in whom inflammatory bowel disease is suspected.
- Microcytic anemia may be a clue to occult GI blood loss.
- Tests to screen for celiac disease.
  - Tissue transglutaminase immunoglobulin A (IgA) antibody or anti-endomysial antibody
  - Antigliadin IgG and IgA are much less specific and not worth the extra cost.
- A comprehensive metabolic profile will rule out rare causes of short stature.
  - Electrolyte disturbances
  - Kidney disease
  - Liver disease

IMAGING

- A bone age film is the only radiographic examination that should be considered.
  - Not very useful as a diagnostic test because most children who are short (aside from genetic short stature) have a bone age delay of ≥1 year.
  - A clinician may order bone age film in a child >7 years to make a height prediction if CGD or FSS is suspected.

TREATMENT APPROACH

- In healthy children at or above the third percentile and growing at a normal rate, the chances of finding a treatable cause for shortness are small.
  - The child should have growth carefully measured and plotted at each visit to make sure it is not dropping below the third percentile.
  - If the parents insist on seeing a specialist, they should be told that their child will not likely need or be eligible for coverage of GH therapy.
- A child who is in the reference range but crossing percentiles.
  - Between 6 and 24 months, such shifts are common, especially in CGD.
  - If the child crosses one percentile channel (eg, from the 25th to the 10th percentile) over ≥3 years, and history and examination are normal, a cause will not likely be found.
  - Children who cross >1 percentile channel in <3 years have a greater chance of having a definable cause for short stature.
    - The most common cause is the use of stimulant medication for attention-deficit/hyperactivity disorder.
- Parents of children short enough to be referred can be told that screening tests and a period of observation are needed before a decision can be made about the need for GH therapy.
- Such children are best referred between the ages of 3 and 6 years.
  - Children who are pubertal or on the verge of puberty do not usually benefit from GH therapy.

SPECIFIC TREATMENT

Human GH

- Children with a history of intrauterine growth retardation (born SGA) who have not caught up to the reference range by age ≥2 years.
  - The US Food and Drug Administration (FDA) has approved use of GH without the need for GH testing.
- Children within reference range in height with a drop-off in linear growth >1 percentile channel over ≤3 years or who have shown documented growth arrest for 1 year may have a definable cause for their short stature that may be responsive to GH or other specific therapy.
- Children with short stature who have not started puberty by age 14 years (occurs mostly in boys with CGD).
  - When the boy is anxious to start his growth spurt sooner rather than later, treatment with a brief course of testosterone injections is appropriate.
- The FDA has approved GH for children ≤first percentile with an anticipated adult height (based on bone age) below the reference range.
- Some insurance companies refuse to cover GH to treat ISS, arguing that no medical condition exists.

WHEN TO REFER

- Children <third percentile, particularly if height is falling further below the reference range over time.
- Children who were born SGA (intrauterine growth restriction) who have not caught up to the reference range by ≥2 years.
- Children within the reference range for height who have dropped off >1 percentile channel over the past ≤3 years or who have documented growth arrest for 1 year.
- Children with short stature who have not started puberty by age 14 years.
- Dysmorphic children with short stature should be referred to a geneticist for a specific diagnosis.
- For children reporting poor self-esteem because they are short, referral to a psychologist may be more helpful than to an endocrinologist.
- If weight gain is persistently poor, referral to a GI or nutrition specialist should be considered.

FOLLOW-UP

- Follow-up of patients with short stature is important before the diagnosis, to establish the growth velocity, and after therapy to monitor its success.

COMPLICATIONS

- Some children with short stature develop significant psychosocial problems, such as poor self-esteem.

PROGNOSIS

- Children with CGD usually end up with heights in the lower half of the reference range.
- Children with FSS tend to achieve adult height within 2–3 inches of their adult target height.
  - Target height is calculated by averaging the heights of the parents and adding 2.5 inches for boys and subtracting 2.5 inches for girls.
- Children with ISS respond variably to GH, with a modest average improvement in adult height.

PREVENTION

- Measuring length and height at each clinic visit, and plotting them on growth curves, can lead to earlier identification of children with short stature.
- Appropriate evaluation and therapy can be instituted sooner for better outcomes.

DEFINITION

- Sinusitis is infection of the paranasal sinuses.

SIGNS AND SYMPTOMS

- Cough and nasal discharge.
  - Cough occurs during the day but may be worse at night when the child is supine.
  - Nasal discharge may be clear or purulent.
- Parents of young children may report fetid breath.
- Headache and facial pain are uncommon symptoms in children with acute sinusitis.
- Occasional painless swelling of the periorbital tissues without erythema.
  - May be confused with periorbital cellulitis in its early stage
- A less common presentation of acute sinusitis is an unusually severe upper respiratory tract infection.
  - Most uncomplicated upper respiratory tract infections improve after 5–7 days.
  - Symptoms that persist without improvement for >10 days suggest bacterial superinfection.
  - In most cases of viral upper respiratory tract infection, fever precedes onset of watery nasal discharge and is associated with constitutional symptoms.
  - Thickening of nasal secretions occurs later in the course, before resolution.
  - High fever and purulent discharge that coexist for ≥3 days suggests acute sinusitis.
- Cough and nasal discharge persisting for >30 days occurs with subacute or chronic sinusitis.
- During physical examination, carefully inspect the nasal mucosa.
  - It will usually be erythematous and swollen.
  - It may be pale and boggy.
- Mucopurulent material can sometimes be seen in the nose or draining into the nasopharynx.
- Palpation or percussion of the sinuses may elicit tenderness.
- Periorbital edema and mild discoloration of the skin below the eyelids is occasionally seen.

DIFFERENTIAL DIAGNOSIS

- The presence of a foreign body in the nose must be ruled out.

DIAGNOSTIC APPROACH

- The distinction between viral infections and acute bacterial sinusitis is based on the persistence and severity of upper respiratory symptoms.

LABORATORY FINDINGS

- Nasopharyngeal culture results correlate poorly with sinus culture results.

IMAGING

- Routine use of radiographs to confirm diagnosis of uncomplicated sinusitis is not recommended in children <6 years.
- Clinicians should not obtain imaging studies of any kind to distinguish acute bacterial sinusitis from viral upper respiratory tract infection.
- However, a contrast-enhanced computed tomography (CT) scan of the paranasal sinuses should be obtained whenever a child is suspected of having orbital or central nervous system complications.

DIAGNOSTIC PROCEDURES

- Transnasal aspiration of the maxillary sinuses can be performed by an otolaryngologist for diagnostic purposes in specific situations.
- Bacteria are present in a sinus aspirate 75% of the time when
  - Clinical signs and symptoms suggest acute sinusitis.
  - Maxillary sinus radiographs show
    - Air-fluid levels
    - Complete opacification
    - Mucosal thickening of ≥4–5 mm
- Sinus aspiration and lavage are indicated only in children who
  - Fail to respond to conventional antibiotic therapy.
  - Are immunosuppressed.
  - Have an illness that is severe or life-threatening.

TREATMENT APPROACH

- Treatment of sinusitis in children involves
  - Antibiotic therapy.
  - Symptomatic relief measures.
  - Drainage, if necessary.
  - The following treatments are recommended to help drain the sinuses:
    - Decongestants
    - Antihistamines
    - Saline nose drops
  - No proof of the efficacy of these agents exists.
  - The American Academy of Pediatrics does not recommend the use of antihistamines and decongestants in children <6 years because of possible side effects and adverse effects due to accidental overdosing.

- Amoxicillin is an appropriate initial choice for treating uncomplicated sinusitis.
  - It is most appropriate in geographic areas where the prevalence of β-lactamase–producing strains of *Haemophilus influenzae* and *Moraxella catarrhalis* is low.
- In communities with a high prevalence of nonsusceptible *Streptococcus pneumoniae* (>10%, including intermediate- and high-level resistance attributable to altered penicillin-binding proteins), higher-dose amoxicillin (80–90 mg/kg/d in 2 divided doses, with a maximum of 2 g per dose) should be considered.
- Macrolide antibiotics are an option for children allergic to amoxicillin or other β-lactam antibiotics.
- Intranasal steroids may provide some benefit, particularly in the second week of therapy.
  - Further research is necessary to define their role in management.

SPECIFIC TREATMENTS

Amoxicillin

- Amoxicillin is the drug of choice for treatment of uncomplicated sinusitis.
- For children who do not respond to amoxicillin, broader coverage should be considered with amoxicillin plus
  - A clavulanate *or*
  - A carbacephem *or*
  - A macrolide *or*
  - A third-generation cephalosporin
- These alternatives should also be considered for the child who has
  - Recently been treated with amoxicillin
  - Frontal or sphenoid sinusitis
  - Complicated ethmoid sinusitis
  - Very protracted symptoms
- Patients who are allergic to amoxicillin may be treated with
  - A carbacephem *or*
  - A macrolide *or*
  - A third-generation cephalosporin

WHEN TO ADMIT

- In unusually severe cases, hospitalization and parenteral antibiotics may be required.

WHEN TO REFER

- Otolaryngological consultation is appropriate in cases for which hospitalization is needed.
- Surgery may be required in cases of medically recalcitrant severe chronic sinusitis in children.
- Patients with recurrent sinusitis or chronic sinusitis associated with immunodeficiencies should be referred to an otolaryngologist or infectious disease specialist.

FOLLOW-UP

- Children who have >2–3 episodes of acute bacterial sinusitis per year should receive evaluation for underlying conditions.
- The first step is a screening evaluation for allergic rhinitis.
  - If results are positive, aggressive environmental controls and medication to reduce allergic inflammation (eg, montelukast, nasal antihistamines, nasal steroids) should be instituted.
- If problems persist, the next step is to exclude a subtle presentation of chronic infection.
  - Low-radiation limited sinus CT (eg, MiniCAT) is quick, noninvasive, sensitive, and safe compared with rhinoscopy, plain radiographs, or traditional sinus CT.
  - A positive study result can help direct sinus lavage and define suboptimal sinus ostial anatomy.
- A poor clinical course despite assessment and treatment of allergic rhinitis and surgical intervention should raise concerns about a humoral immunodeficiency.
  - Particularly if the child also suffers from recurrent otitis media, bronchitis, and pneumonia.
  - Baseline screening evaluation includes quantitative immunoglobulins (IgG, IgA, IgM, IgE), complete blood cell count with differential, and CH50.
  - Secondary tests include assessment of specific antigens (eg, unconjugated pneumococcal vaccine).
- For the child who has recurrent sinusitis and no underlying disorder
  - Some recommend antibiotic prophylaxis.
    - — No scientific studies support this practice.
    - — May lead to rapid development of antibiotic resistance.

COMPLICATIONS

- Complications of sinusitis are most often due to local extension of the disease.
  - Orbital cellulitis is the most common serious complication.
    - — In many cases, it lacks the common symptoms of sinusitis.
    - — The eyelids appear intensely red and swollen.

  - Fever, malaise, and an increased leukocyte count are present.
  - To distinguish this condition from preseptal (periorbital) cellulitis, evaluate the child for
    - Orbital pain
    - Proptosis
    - Limitation of eye movement (ophthalmoplegia)
    - Diminished visual acuity
  - CT may be needed for differentiation.
  - This complication has been reported most frequently in male adolescents.
- Intracranial infection is the second most common complication.
  - Subdural empyema (most common)
    - Low-grade fever.
    - Malaise.
    - Frontal headache.
    - As the disease progresses
      - Vomiting
      - Decreased level of consciousness
    - Infection can occur by direct extension through necrotic bone or by bacterial spread through the venous system.
    - Peak age of incidence of this complication is between 10 and 20 years, but it can develop in younger children.
- If a patient is thought to have an intracranial abscess
  - Head CT with contrast should be obtained.
  - Lumbar puncture should be avoided until intracranial mass effect has been ruled out.
  - Immediate treatment with high-dose parenteral antibiotics.
  - To drain the abscess and to debride necrotic bone
    - Neurosurgery should be consulted.
  - Steroids and hypertonic agents (mannitol or glycerol) may be necessary to control intracranial hypertension.
- Other, less common complications include
  - Meningitis
  - Osteomyelitis of the frontal bone (Pott puffy tumor)
  - Epidural abscess
  - Cavernous sinus thrombosis

PROGNOSIS

- Clinical improvement should be expected within 48 hours after treatment is initiated.
- A minimum of 10 days of antibiotic therapy usually is adequate.
  - If symptoms fail to resolve completely within 10 days, patients should be treated for an additional 7 days beyond the resolution of symptoms.

PREVENTION

- If the patient is known to have allergic rhinitis, environmental controls, antiallergic medications, and/or referral to an allergist may help prevent recurrent sinusitis.
- Chronic prophylactic antibiotic use did not prove to be successful in preventing recurrent sinusitis.

DEFINITION

Maturational or Behavioral Issues

- Average sleep by age is seen in **Table 1.**
- Day-night reversals: usually occurs at ~2 weeks of age.
- Settling: 5 hours of continuous sleep after midnight for 4 consecutive weeks.
- Sleep-onset associations: Conditioned response; child cannot fall asleep unless established conditions associated with sleep onset are recreated.
- Limit-setting disorder: Bedtime routines >30 minutes may reflect parental difficulty in setting limits.
- Bedtime fears: most often seen in preschool and early school-aged children.
- Primary insomnia: Must last at least 1 month, interfere significantly with functioning or cause significant distress, and not be part of another medical, sleep, or mental disorder.
- Dyssomnia: insomnia that does not meet disorder criteria; includes environmental sleep disorder commonly caused by noise, pets, and temperature extremes.
- Awakenings from sleep: problematic only when the child cannot return to sleep on his or her own.
- Sleep-onset association disorder.
  - Trained night feeding: infants >6 months who wake up during the night and are immediately fed to encourage return to sleep
  - Trained night waking: waking between 4 and 8 months of age without requiring a feeding
  - Developmental night waking: infants who slept through the night by 6 months but begin awakening again at around 8–10 months of age

Sleep-Related Breathing Disorder

- Snoring is common; obstructive sleep apnea is less common.

Circadian Rhythm Sleep Disorder

- Sleep-phase delay, commonly seen in adolescents

Parasomnias (Disorders of Partial Arousal From Slow Wave Sleep)

- Unusual behaviors or experiences that occur during sleep or the transition between sleep and waking
  - Confusional arousals: Child appears awake but is confused and nonresponsive to parental questions.
  - Sleep terrors: characterized by physiologic arousal, including pallor, sweating, pupillary dilation, piloerection, and tachycardia.
  - Sleepwalking disorder (somnambulism): occurs mainly during first 120 minutes of sleep.
  - Nightmare disorder: occurs during rapid eye movement (REM) sleep, usually during last one-third of sleep period.
  - Violent behavior during sleep: Normal REM atonia does not occur and dream content can be physically acted out, sometimes violently.
  - Bruxism: grinding of teeth during sleep.

Table 1. Average Sleep by Age

Age	Total Sleep Duration (h)	2%–98%	Mean Daytime Duration (h)	Daytime Napping Children (%)
1 mo	14.0	9.0–19.0	5.5	100
3 mo	14.0	10.0–18.5	5.0	100
6 mo	14.2	10.4–18.1	3.4	100
9 mo	13.9	10.5–17.4	2.8	100
12 mo	13.9	11.4–16.5	2.4	100
18 mo	13.6	11.1–16.0	2.0	96
2 y	13.2	10.8–15.6	1.8	87
3 y	12.5	10.3–14.8	1.7	50
4 y	11.8	9.7–14.0	1.5	35
5 y	11.4	9.5–13.3	0	8

Sleep-Related Movement Disorders

- Restless legs syndrome: uncomfortable sensations in the legs, worse at rest ("like worms crawling under my skin")
- Periodic limb movements of sleep: repetitive, brief leg twitches, occurring >5 times per hour
- Sleep-wake transition disorder: rhythmic movements while falling asleep, common in infants and toddlers

Hypersomnia

- Narcolepsy: potentially disabling syndrome of irresistible daytime sleep attacks, abnormally fast transitions to REM sleep from awake, and disrupted nighttime sleep
- Idiopathic hypersomnia: constant and severe excessive daytime sleepiness despite adequate nocturnal sleep

Sleep Disorders Associated With Psychiatric or Behavioral Disorders

- Most common in mood disorders

Developmental Disorders

- Learning disabilities are associated with increased rates of sleep disturbance, including night waking and trouble falling asleep.

Sleep Disorders Associated With Medical Problems

- Neurologic disorders: central nervous system (CNS) impairment that results in dysregulation of the sleep cycle.
- Sleep-related epilepsy: ~20% of epileptic patients have seizures only during sleep, most often during sleep-wake transitions.
- Sleep-related headaches: usually during REM sleep.
- Degenerative disorders.
- Sleep-related asthma.
- Gastroesophageal reflux disease (GERD).

SIGNS AND SYMPTOMS

- Inadequate amount of sleep.
  - Excessive daytime sleepiness (rare in young children)
  - Hyperactivity—impaired attention
  - Poor school performance—impaired concentration, vigilance
  - Behavior problems—bad mood, irritability
  - Obesity—possible link to inadequate sleep
  - Failure to thrive
- Circadian rhythm disorder.
  - In adolescents: late sleeping on weekends followed by difficulty sleeping at regular hours
- Parasomnias (partial arousal disorders): Child not fully awake, does not remember the event in the morning.
  - Confusional arousal
    - Partial arousal from slow wave sleep, during which children sit up, mumble, and appear awake.
    - Confusion, nonresponsive to parental questions.
    - Children may thrash about and respond combatively.
  - Sleep terrors
    - Physiologic arousal including pallor, sweating, pupillary dilation, piloerection, and tachycardia.
    - Child may sit up and scream and may appear terrified.
    - Child may thrash or run and is not responsive to attempted parental comforting.
    - Tends to occur over several weeks and then disappear and recur several weeks later.
  - Sleepwalking disorder (somnambulism)
    - Child difficult to arouse, uncoordinated, and wandering in illogical places
- Restless legs syndrome.
  - Present in the evening
  - Associated with the need to move and temporarily relieved by movement
- Periodic limb movements of sleep.
  - Leg movements or jerks with resumption of breathing after apnea
- Sleep-wake transition disorder.
  - Monotonous head banging, occurring 60–80 times per minute, usually for <15 minutes
- Hypersomnia.
  - Child appears to have difficulty remaining awake and may exhibit hyperactivity, restlessness, poor concentration, impulsivity, aggressiveness, or irritability.
- Narcolepsy.
  - Triad seen in 30% of patients
    - Loss of muscle tone with emotions while awake (cataplexy)
    - Inability to move for a few seconds to minutes on awakening (sleep paralysis)
    - Visual aura or dream states while falling asleep (hypnagogic hallucinations); excessive daytime sleepiness

- Degenerative disorders.
  - Frequent awakenings, difficulty falling asleep, early morning waking, sleep deprivation, and daytime sleepiness

DIFFERENTIAL DIAGNOSIS

- Circadian rhythm disorder
  - Differentiate from oppositional disorder by the child's behavior pattern.
  - A child with a circadian rhythm disorder may not resist going to bed but is unable to fall asleep.
- Violent behavior during sleep
  - Abnormal behaviors occur during the last one-third of the night, unlike non-REM motor parasomnias, which typically occur during first one-third of the sleep period.
- Hypersomnia
  - Differentiate from weakness or fatigue.
- Narcolepsy
  - Differential diagnosis includes
    - Hydrocephalus
    - Postviral infection (mononucleosis)
    - Previous CNS trauma
    - Idiopathic hypersomnia
- Idiopathic hypersomnia
  - Other causes of hypersomnia include
    - Neurologic disorders (hydrocephalus or CNS tumors)
    - Primary sleep disorders (obstructive sleep apnea)
    - Mood disorders
    - Chronic fatigue syndrome
    - Medical disorders (acute and chronic infections, including mononucleosis, metabolic disorders, or muscle diseases)
- Sleep-related headaches
  - Evaluate for increased intracranial pressure or hypercapnia caused by hypoventilation (eg, Duchenne muscular dystrophy).
- GERD
  - Diagnosis not obvious if usual signs are not evident (excessive spitting up, re-swallowing motions, increased fussiness, refusal of feedings, and failure to thrive)

DIAGNOSTIC APPROACH

- Parent or other caregiver usually initiates the diagnostic evaluation.
- Most common complaints include
  - Inability to fall asleep or remain asleep
  - Daytime sleepiness
  - Abnormal behaviors during sleep
- History is the major initial diagnostic tool.
  - General medical, developmental, and mental health, including medications, herbal products, drugs, alcohol, or tobacco use
  - Parental sleep history
  - Parental perceptions and differences of opinion about sleep
    - Co-sleeping
      - When agreeable to both parents, not associated with behavioral or emotional problems
      - If a source of discord or reflecting parent's inability to manage the child's behavioral bedtime problems, should be addressed
  - Parental mental health
  - Observations by babysitters or relatives
  - Family-provided audiotapes or videotapes
- Questionnaires
  - BEARS (**b**edtime problems, **e**xcessive daytime sleepiness, **a**wakenings at night, **r**egularity and duration of sleep, and **s**noring) can help the practitioner to
    - Determine the level of parental concern.
    - Elicit maladaptive patterns if no concern is expressed.
    - Help formulate a differential diagnosis.

LABORATORY FINDINGS

- Haplotyping, karyotyping, or fluorescent in situ hybridization studies for diagnosing genetic conditions.
  - Congenital central hypoventilation syndrome
  - Rett syndrome
  - Smith-Magenis syndrome
  - Prader-Willi syndrome
- ~ 90% of patients with narcolepsy with cataplexy are positive for HLA-DQB1*06:02.
  - Absence does not exclude the diagnosis of narcolepsy, especially without cataplexy.

IMAGING

- Violent behavior during sleep
  - Diagnosis requires a sleep study and neuroimaging.

DIAGNOSTIC PROCEDURES

Sleep Study

- Overnight study includes
  - Electroencephalography to identify sleep stages
  - Electromyelography of chin activity to help identify decreased tone during REM sleep

- Leg electromyelography to measure leg movements
- Electrooculography to identify eye movements seen in REM sleep
- Electrocardiography to monitor cardiac rate and rhythm
- Nasal and oral thermistors to measure airflow
- Thoracic and abdominal belts to measure chest and abdominal movements during breathing
- Pulse oximetry to measure oxygen saturation
- End-tidal carbon dioxide monitoring to indirectly measure hypoventilation

■ Extended-montage video electromyelography may be incorporated into the polysomnography to diagnose nocturnal seizures.

Sleep-Related Breathing Disorder

■ Whether all children should have sleep studies before adenotonsillectomy is controversial.

■ Certain groups are at higher risk for perioperative complications and may warrant polysomnography as part of a preoperative evaluation, especially if outpatient surgery is being contemplated.
- Age <3 years
- Morbid obesity
- Chromosomal or craniofacial anomalies
- Underlying neuromuscular disorders
- Other underlying medical conditions that increase surgical risk

Actigraph

■ Actigraph is a small portable device similar to a large wristwatch, worn for several weeks.

■ Can be a useful, noninvasive method for assessing specific sleep disorders.
- Insomnia
- Excessive daytime sleepiness
- Circadian rhythm disorders

SPECIFIC TREATMENTS

Maturational or Behavioral Issues

■ Day-night reversals
- Establish a general bedtime.
- Keep lights off or low.
- Keep interaction to a minimum during nighttime feedings.
- In the morning, keep lights bright and encourage social interaction.

■ Sleep-onset associations
- Advise parents to place the infant into the crib while infant is still awake for night and naps starting by 48 weeks' post-gestational age.
- If a problematic sleep-onset association has already developed, parents may need to institute a graduated program.
  - — Warn parents about what to expect and address fears about harming or creating a sense of abandonment.
  - — Success requires consistency and collaboration of all nighttime caregivers.

■ Limit-setting disorder
- Reasonable daily schedules.
- Assurance of adequate special individual time with each parent every day.
- Careful limit setting.
- Limit bedtime routine to a defined set of activities or length of time.
- Notify the child that parents will not respond to further requests, or say "only one more" and adhere to this declaration.
- Set bedtime for when the child is tired to enhance the child's tendency to fall asleep.
- Avoid naps close to bedtime.
- Use positive reinforcement.

■ Bedtime fears
- Acknowledge child's fears.
- Reassure child that the parents will be able to keep the child safe.
- Consider ritual of the adult spraying for monsters.
- Have the child help the parent buy a special flashlight to use to check out the room at night.
- Relaxation exercises and empowerment stories for older children.
- Nightlight.

■ Primary insomnia
- Eliminate distraction or correct environmental conditions.
- Diphenhydramine, clonidine, and melatonin have been used.
  - — Indiscriminate medication can mislead about the causes of insomnia or prevent behavioral management.

■ Sleep-onset association disorder
- Trained night feeding
  - — Formula-fed infants who have learned to sleep through the night and subsequently begin waking hungry are probably ready for solids (if >4–6 months) or need increased feeding during day or evening.
  - — Breastfed infants may respond to more frequent evening feedings (cluster feeding).

- Trained night waking
  - Management of the precipitant stress with collaboration with spouse or neighbors to tolerate some crying during treatment.
  - Establish bedtime routines, perhaps with infant clothing with a maternal scent.
  - Place infant into bed awake.
  - Limit daytime naps to 2 hours to consolidate longest sleep period at night.
  - Allow 1–2 minutes of crying before being checked, but not fed, and then check every 2–5 minutes.
  - Do not pick up, rock, or cuddle infant; touching is OK.
  - May require the more involved parent to take a shower, turn up music, go out of the house, or find some other distraction.
  - Brief sedation with diphenhydramine for the infant should rarely be needed to help modify this habit.

- Developmental night waking
  - Advise parents at the 6-month health supervision visit to expect a recurrence of night waking.
  - Advise parents to wait a few minutes before going in to the infant but to avoid feeding or other reinforcement.
  - If waking is already established, explain contributing forces and advise parents to create a bedtime routine, including a transitional object and a dim nightlight.
  - When the infant awakens, give at least 2 minutes to self-soothe, with some fussing tolerated as part of the process.
  - If fussing continues, one parent can go to reassure the infant briefly, without touching or feeding, and settle down within sight to sleep the rest of the night without talking to the infant.
  - The infant often becomes enraged instead of fearful, which is more tolerable to the parent, who can see that the infant is safe.
  - For children who are no longer constrained to a crib, the parent must prevent body contact with the child by giving the child the alternative that the parent will leave the room to avoid establishing a sleep association.
  - Further interactions should be brief and minimally interactive.
  - Eventually, the child will no longer require the parent's presence to return to sleep after nocturnal awakenings.

Sleep-Related Breathing Disorder

- Many improve after adenotonsillectomy; those with obesity or asthma are less likely to experience complete resolution.
- Nasal continuous positive airway pressure (CPAP) or even tracheostomy may be required.

Circadian Rhythm Disorder

- Changing adolescent sleep-phase delay requires intense commitment and active participation of the adolescent and parents.
- Use bright light exposure in the morning and consistent wake times all 7 days of the week.
- Adjust different types of circadian shift by simultaneously shifting naps, bedtime, waking time, and meals to a desired schedule.

Parasomnias (Partial Arousal Disorders)

- Confusional arousals
  - Reassure parents that episodes are generally benign.
  - Provide minimal intervention during episodes.
  - Remove potential safety hazards from the child's bedroom.
  - Treat disorders that may fragment sleep, such as obstructive sleep apnea and restless legs syndrome.
  - In severe cases, a few weeks of a benzodiazepine, such as lorazepam, at bedtime may interrupt the sequence by reducing slow wave sleep.
    - Rebound occurs with discontinuation of the medication, often with an increasing number of events.
- Sleep terrors
  - Empty bladder routinely before bedtime.
  - Keep environment dark and quiet.
  - Bouts may be interrupted by waking the child 15 minutes before expected episode, generally ~1 hour into sleep each night for approximately a week.
  - A 30- to 60-minute afternoon nap can reduce the depth and amount of stage 4 sleep and may decrease the number of episodes.
  - Treatment with benzodiazepines can reduce the frequency of these events by altering slow wave sleep, but episodes may recur with weaning or tolerance.
- Sleepwalking disorder (somnambulism)
  - Safeguard chronic sleepwalkers to prevent injury.
  - Door and window alarms and locks may be necessary.

- Nightmare disorder
  - Comfort a child who wakes from a frightening dream.
  - Keep intervention brief to avoid secondary gain.
  - Follow recommendations for bedtime fears.
  - Chronic nightmares improve with targeted relaxation exercises and stories in which the child masters a situation.
  - Prepare for good dreams through rehearsal and imaging at bedtime.
  - Severe nightmares may respond to bedtime medications, although counseling is mandatory.
- Violent behavior during sleep
  - Treatment with clonazepam has been beneficial in children with autism spectrum disorder (ASD).
- Bruxism
  - Tooth guards can protect the teeth and reduce potential damage to the temporomandibular joint.
  - Relaxation exercises at bedtime if stress or anxiety is a trigger.

Sleep-Related Movement Disorders

- Restless legs syndrome and periodic limb movements of sleep
  - Iron supplements, clonidine, gabapentin, or dopaminergic agents, depending on child's age
- Sleep-wake transition disorder
  - Reduce condition by kinesthetic stimulation during the evening and holding the child as part of the bedtime routine.
  - Sleep restriction (ie, limiting the time the child lies in bed before falling asleep) and mild sedation are helpful in difficult cases.
  - Parents often need reassurance of the generally benign nature of these behaviors.

Hypersomnia

- Narcolepsy
  - Stimulants, such as modafinil or methylphenidate, to address excessive daytime sleepiness.
  - Antidepressants, such as venlafaxine, to control cataplexy.
  - Regular adequate sleep.
  - 2–3 planned 30-minute daytime naps.
  - Time activities at optimal hours of alertness.
  - Educate patient, family members, and school personnel.
- Idiopathic hypersomnia
  - Attention to sleep hygiene
  - Stimulant medications
  - Review of safety issues, such as driving or operating machinery

Sleep Disorders Associated With Psychiatric Behavioral Disorders

- Depression
  - Cognitive-behavioral therapy
  - Antidepressants

Developmental Disorders

- Clonidine at bedtime improved the sleep of 85% of affected children when behavioral measures failed.
- Children with ASD frequently have insomnia that may benefit from behavioral interventions, melatonin, or medications.

Sleep Disorders Associated With Medical Problems

- Neurologic disorders
  - Establish a bedtime routine and put the child to bed when sleep onset is likely to occur quickly.
  - If the child has persistent difficulty, establish a new pattern by delaying the usual bedtime for 30 minutes and then removing the child from bed if sleep does not occur in 15–20 minutes.
    - After removing the child from bed, keep him or her awake for 30 minutes.
    - Repeat until the child falls asleep within 15 minutes.
  - Keep wake-up time constant.
  - Do not allow daytime naps for children >4 years.
  - Melatonin at bedtime.
    - Use cautiously in children with seizure disorders.
- GERD
  - Holding the child upright reduces the amount of acid in the esophagus and may comfort a child.

WHEN TO ADMIT

- Primary sleep disturbances rarely require hospitalization, other than the overnight stay for a sleep study.
- Exceptions may include
  - Severe sleep-disordered breathing with life-threatening oxygen desaturations
  - Arrhythmias
  - Cor pulmonale
  - CNS tumors
  - Serious depression

WHEN TO REFER

- If the clinician is unable to relieve a sleep disturbance after working with the family over the course of 6 weeks, assistance may be needed from a sleep specialist, family therapist, or psychologist.

- Children with chronic, physically based sleep disorders, such as narcolepsy and sleep-disordered breathing, requiring CPAP.

PREVENTION

- Establish a good sleep environment.
  - Dark, quiet, and comfortable.
  - Steady, slightly cool temperature.
  - Sleep should be in the same place for night and naps as much as possible.
    - — Use bed or crib for sleep and not as play area while awake.
- Establish a soothing bedtime routine.
  - Snack, toothbrushing, use of the toilet, and then story, prayer, or talking time with children in their own bed.
  - Leave the room while the child is still awake.
  - Feed infants in a parent's arms and place in the crib without a breast or a bottle.
  - Avoid excessive feeding close to bedtime to reduce the need to void during the night.
  - Put children to bed when they are moderately tired to reduce bedtime resistance.
- For children whom the parents would like to have sleep in their own crib, avoid pacifiers or body contact with the parent as they drift to sleep (self-soothing).
- Avoid changing the routine because of demands or tantrums that can develop into a pattern.
- Keep television, computer, and any other electronic screens out of the child's room.
- Enforce an electronic curfew for older children and adolescents to prepare for sleep without distraction and prevent use during the night without parental supervision.
- Try to keep a consistent schedule for bedtime, naps, and morning wake up, to help the child maintain regular circadian rhythms.
- Try to keep the household atmosphere calm in the evening.
- Keep track of activities that seem to lead to sleeping problems.
- Avoid caffeine at least 6 hours before bedtime.

DEFINITION

Language

- Primary vehicle for communication.
- Socially shared code or conventional system for representing concepts through an arbitrary set of rule-governed symbols (speech sounds/phonemes) and symbol combinations.
- Social tool through which we share ideas and rules of behavior and develop our attachments to people and places.
- Rule-governed yet generative system that permits speakers to create an endless number of meaningful utterances to communicate thoughts, feelings, information, and ideas.
- Receptive language generally develops in advance of expressive language, except in rare circumstances (eg, hydrocephalus, severe language processing disorder, autism spectrum disorder [ASD]).

Language Disorder

- Any disturbance to an individual's ability to develop and produce spoken or written language.
  - Ability to comprehend
  - Ability to express language at an age-appropriate level
- Developmental and acquired disorders represent a heterogeneous set of difficulties that range from mild to severe.
- Receptive language deficits.
  - Difficulty comprehending language.
  - Rarely seen in isolation.
  - In typical development, comprehension precedes expression of new and more mature language forms.
  - Manifest as reduced understanding of conversation and problems with following directions.
- Expressive language deficits.
  - Problems using language to express basic wants and needs as well as more sophisticated thoughts, feelings, and intentions.
  - Difficulty putting words into sentences.
    - Simple, short sentences with confused syntax or verb tense errors
    - Difficulty finding the right words
  - Vocabulary below the level of children the same age.
  - Child might use words and phrases repetitively or pick up scripts from videos, commercials, and television.
  - Language impairment might also become apparent as a deficit in stringing sentences together to tell a cohesive story or personal narrative.

Speech Disorders

- Manifest as articulation errors past the age of expectation
  - Articulation: movement of the speech mechanism (palate, lips, tongue, jaw, larynx) to create sound
    - Example: lisp
  - Phonology: rule system that governs how speech sounds interact with one another
    - Example: substitution of all K sounds with T ("otay" for "OK")
- For pediatricians, knowing when to refer for evaluation is key. As a guideline, in communication with a stranger
  - 2-year-old should be 50% intelligible.
  - 3-year-old, 75%.
  - 4-year-old fully intelligible to a stranger.

HISTORY

- Normal developmental milestones are in **Table 1.**
- Risk factors for language delays are similar to those for developmental disorders in general.
  - Family history of speech and language delay
  - Male sex
  - Perinatal factors
  - Educational level of the parents
  - Childhood illness
  - Family size
- To determine children at greater risk, ask about
  - Prenatal, perinatal, or postnatal adverse events
  - Family history
    - Developmental disorders
    - Academic achievement
    - Social functioning
- For warning signs by age, see **Table 2.**
- Language delays may present as problems with
  - Oral language, reading, spelling, or writing
  - Expressing ideas, finding words, learning new vocabulary, comprehending questions, following directions, and retaining written material
  - Learning the alphabet, spelling rules, multiplication tables, and other rote-memorized information, all of which make it difficult to achieve academically

Table 1. Developmental Milestones

Age	Milestone
0–6 mo	Cooing Babbling Differentiated cries
6–9 mo	Canonical babbling (eg, "babababa") Response to name Comprehension of familiar words in context
9–15 mo	First words Directed point (initially with hand, and then with one finger)
18–24 mo	Uses own name 2-word sentences (by 24 mo) Knows 5 body parts
24–30 mo	Pretend play with familiar objects 3-word sentences Points to action words in pictures Answers simple, concrete "wh" questions (eg, who, what) Uses 50+ words
30–36 mo	Names most familiar things and pictures Begins to recognize same and different Helps tell a familiar story Uses descriptive words (adjectives) Uses 200–1,000 words Speech is nearly intelligible to any listener.
3–4 y	Comprehends 1,000 words Points to common object by function Responds to commands involving 2 actions Uses ≥800 words Responds to simple "how" questions Asks "what" and "who" questions Uses plurals and verb tense markers Talks about events out of the here and now
4–5 y	Understands most of what is said to him or her Tells a personal story with a beginning, middle, and end Can listen and answer questions about a story Speech is fully intelligible. Can recognize and produce rhymes

Table 2. Red Flags in Language and Play

Age	Warning Signs and Red Flags
0–12 mo: play	Restricted repertoire of skills Does not follow objects that fall Little purposeful play Reduced or absent imitation Reduced object permanence No interactive games
0–12 mo: sensory motor	Does not reach for or swat at objects Overly reactive to stimuli Extreme irritability
0–12 mo: socioemotional	Overly clingy No apparent attachments No awareness of danger Difficulty modulating emotions Reduced range of affect
0–12 mo: speech and language	Difficulty sucking and feeding Averts gaze Fails to make variety of sounds Fails to respond to name Undifferentiated crying
12–24 mo: play	No container play No early problem-solving Does not go to adults for help Very rigid play Focuses on irrelevant parts of toy, such as wheels of car Does not include adults in play; prefers to play alone No interest in playing symbolically No spontaneous/pretend play Restricted range of interests
12–24 mo: socioemotional	Short attention span Does not seek to engage with others Tunes out Avoids eye contact
12–24 mo: speech and language	No specific "mama" or "dada" Does not point Cannot follow simple directives without gesture Reduced vocabulary No word combinations

Table 2 (*continued*)

Age	Warning Signs and Red Flags
24–36 mo: play	Little or no symbolic play Not able to sequence events in play Not interested in playing with peers Restricted range of skills and interests Lines up toys rather than playing with them
24–36 mo: speech and language	Avoids eye contact Reduced communicative intent Difficulty following directions Lack of verbal expression Reduced reciprocity and turn taking Talking better than listening Poor conversation skills
3–4 y: play	Cannot take turns or play cooperatively with peers (prefers solitary play) Little interest in toys Insists on sameness in routine No idea how to approach new skills or toys Cannot use blocks to build simple structures
3–4 y: language	Does not engage in back-and-forth communication for purely social reasons Does not talk about what communicative partners are talking about Uses language that is repetitive or recycled from other contexts
4–5 y: play	Cannot follow simple rules in play Prefers solitary play Insists on sameness in play Reacts strongly to change Does not engage in symbolic or imaginative play
4–5 y: language	Weak ability to hold a conversation Cannot tell a personal narrative Difficulty with sequencing information Uses language that is repetitive or recycled from other contexts

DIFFERENTIAL DIAGNOSIS

- Delays in speech and language are often the first indication of the presence of a developmental disorder or disability.
- Hearing loss is an important consideration in any child who exhibits delayed acquisition of language milestones or unclear or atypical patterns of speech.
- Apraxia.
  - Motor speech disorder caused by a difficulty planning and executing speech sounds; not attributed to muscle weakness or paralysis.
  - Limited repertoire of vowels and vowel errors.
  - Error patterns are typically highly variable and idiosyncratic.
  - Errors increase with length and complexity of utterances.
  - Early evaluation and treatment may result in better outcomes.
- Stuttering or dysfluency.
  - Breaks in fluency that can affect sounds, syllables, or words.
  - A period of normal dysfluency may be seen between 2 and 4 years of age.
- Joint attention.
  - Evidenced by gaze sharing or pointing.
  - Documented as early as 8–10 months of age.
  - Absence suggests the possibility of an ASD.
- Any child with significant exposure to a second language or dialect is considered bilingually exposed.
  - Child must be evaluated by a bilingual speech-language pathologist in both languages to determine presence or absence of language impairment.
  - Bilingually exposed children may go through a short period of language loss, especially if recently exposed to a new language.
  - There may be a delay in mastering some grammatical aspects of both languages, and vocabulary may be judged to be insufficient if words in both languages are not considered.
  - Important to determine the dominant language when initiating therapy.

DIAGNOSTIC PROCEDURES

- Order a formal hearing test to be done by an audiologist.
- Do not delay therapy pending definitive audiologic evaluation; it may take months for an uncooperative child to have a hearing test completed.

TREATMENT APPROACH

- Some errors are developmental and will resolve in time; others will need intervention.
- Once a speech or language delay is suspected, refer for diagnostic evaluation to
  - Determine the extent of impairment.
  - Characterize the nature of the disability.
  - Suggest strategies for intervention.

WHEN TO REFER

- Once a speech or language delay is suspected
  - Referral for early intervention evaluation (from birth–3 years of age) or US Department of Education (≥3 years) offers a means of evaluation within a mandated time frame and services based on the evaluation results.
  - Ideally, multidisciplinary team, with speech and language pathologist playing a key role, evaluates
    - Ability to comprehend directions, stories, and other communication.
    - Vocabulary, grammar, and syntax and use of language for a variety of purposes.
    - In certain circumstances, speech sound development, literacy skills, writing, reading comprehension, and fluency.
    - Formal testing with standardized instruments should always be considered.
- Stuttering (dysfluency)
  - Base decision to refer for evaluation on
    - How long dysfluency has persisted
    - Family history
    - Type of repetitions
    - Secondary behaviors
  - Indications for evaluation
    - Persistence for >6 months.
    - Family history of stuttering.
    - Awareness of difficulty.
    - Anxiety or frustration related to speaking.
    - Dysfluent speech to fluent speech is >10% of the overall communication.

PROGNOSIS

- Based on their presentation and degree of severity, language disorders may resolve with intervention by the time a child enters the early school years.
- More often, they persist to some degree for the lifetime of the individual.
- Children identified with speech or language delays in toddler and preschool years are at special risk for behavioral difficulties and problems with socializing.

- Communication difficulties are associated with externalizing disorders (attention-deficit/hyperactivity disorder, oppositional-defiant disorder) and internalizing disorders (anxiety disorders, depression).
- The link between early language and later learning problems is also well documented.
- Children identified with communication impairments at age 4–5 years are likely to have significantly more difficulty in reading, writing, and overall academic achievement at 7–9 years.
- These children have more difficulty with peer relationships and less satisfaction with school than their peers.
- A multitude of factors determines the outcome of children with speech and language impairments.
  - Nonverbal intelligence
  - Type and degree of language disability
  - Response to intervention
- Preschool-aged children with primarily expressive phonologic impairments tend to have a lower risk for later reading problems than those with problems with phonologic awareness (eg, rhyming, letter-sound association).
- Children with language problems that persist until kindergarten entry have a high risk for continuing problems throughout the school years.
- To mediate effects of language delay
  - Provide a language-rich environment, stressing verbal interaction and literacy.
  - Use specific therapy (eg, Reach Out and Read).

DEFINITION

- *Neural tube defects* are congenital defects of the head and spine. They include
  - Head
    - Anencephaly
    - Cranial meningocele
    - Encephalocele
  - Spine
    - Spina bifida occulta
    - Occult spinal dysraphism
    - Meningocele
    - Myelomeningocele
- *Spina bifida* refers to splitting of the vertebral arches.
  - May be associated with protrusion of the meningeal sac.
  - The term *spina bifida occulta* is used when the split is isolated.
- *Meningocele:* protrusion of the meningeal sac between the split vertebral arches.
- *Myelomeningocele:* portions of the spinal cord or spinal nerves contained within the meningeal sac (frequently used interchangeably with the term *spina bifida*).

SIGNS AND SYMPTOMS

- The diagnosis of myelomeningocele is confirmed after birth.
- Inspection of the back to determine the size and location of the open neural placode defect.
- Neurologic and orthopedic examination to assess
  - Rectal tone and anal wink
  - Functional and anatomic levels
  - Spinal and limb deformities
- 4 major malformations account for findings in myelomeningocele (**Table 1**).
  - Soft tissue
  - Vertebral body
  - Spinal cord
  - Brain
- Hydrocephalus.
  - Extremely common; seen in 10%–25% of children with myelomeningocele before or at birth
  - Clinical features (also seen in shunt malfunction) include
    - Bulging fontanel
    - Head circumference beyond growth chart
    - Cranial nerve dysfunction

DIFFERENTIAL DIAGNOSIS

- Myelomeningocele
  - Open lesion or one covered by a thin membrane
  - Meningocele if no nervous tissue in the sac
- Occult spinal dysraphism
  - Tuft of hair
  - Hemangioma
  - Red birthmark
  - Sinus tract or dimple
  - Lipoma
- Caudal regression
  - Lower portion of body is underdeveloped.

DIAGNOSTIC APPROACH

- Classification by
  - Anatomic level where lesion occurred
  - Motor level: what muscles are innervated well enough to perform muscle contraction for activities

LABORATORY FINDINGS

- Prenatal diagnosis.
  - Elevated α-fetoprotein (AFP) on triple or quadruple screening
- Serum blood urea nitrogen and creatinine levels should be obtained as a baseline assessment of renal function.
- As the child grows, urinalysis and urine cultures should be performed as indicated.

IMAGING

- Fetal imaging if maternal AFP is high to identify abnormalities of head and spinal column
  - Ultrasonography
    - Concave shape of frontal calvarium (the lemon sign)
    - Posterior convexity of the cerebellum (the banana sign)
  - Magnetic resonance imaging (MRI)
- After birth
  - Ultrasound
    - Of head to monitor hydrocephalus
    - Hip for subluxation
    - Kidneys and bladder
  - MRI of brain and spine
    - Arnold-Chiari malformation
    - Spinal cord abnormalities (eg, diastematomyelia, diplomyelia, myeloschisis, hypoplastic cord)
  - Plain radiograph
    - Spinal deformities
  - Dynamic voiding cystourethrogram studies

Table 1. Malformations Associated With Myelomeningocele

Soft Tissue	Vertebral	Spinal Cord	Brain
Lipoma	Split vertebral arches[a]	Split cord (diastematomyelia)	Arnold-Chiari malformation[b]: caudal displacement of the cerebellar tonsils, pons, and medulla (may also include brain stem kinking, aqueductal stenosis or forking, or breaking of the tectum)
Fatty filum terminale	Absent vertebrae Fused vertebrae Butterfly vertebrae Wedge vertebrae Scoliosis Kyphosis	Flattened malformed cord (myeloschisis) Hypoplastic cord Duplicate cord (diplomyelia) Low-lying conus Hydromyelia	Polymicrogyria Heterotopia Dysgenesis or agenesis of the corpus callosum Hydrocephalus[c]

[a] Split vertebral arches are necessary for diagnosis.

[b] Arnold-Chiari malformation is almost always present.

[c] Hydrocephalus is identified in 80%–90% of cases.

- Follow-up studies to monitor hydrocephalus
  - Computed tomography or rapid sequence MRI to assess size of ventricles or possible shunt malfunction

DIAGNOSTIC PROCEDURES

- If AFP is elevated, some centers recommend amniocentesis to measure acetylcholinesterase.
  - Potential risk of miscarriage prevents some women from pursuing amniocentesis.

TREATMENT APPROACH

- Goals: Maximize health and independence and minimize disability.
- Requirements.
  - Diligent surveillance
  - Careful and thoughtful interventions
  - Strong interdisciplinary team

SPECIFIC TREATMENTS

- Closure of myelomeningocele.
  - Most undergo postnatal primary closure within 72 hours of elective cesarean delivery.
    - — Experienced pediatric neurosurgeon
    - — Tertiary care center with neonatal intensive care unit experienced with myelomeningocele
  - Fetal repair.
    - — A multicenter trial comparing repair before 26 weeks' gestation with standard postnatal repair found improved motor function and reduced need for shunting at 1 year of age in the fetal repair group.
  - Wound requires monitoring and protection.
- Monitoring for progression of hydrocephalus.
  - No consensus on shunting criteria; reported rates vary by center from 50%–95%.
  - Some neurosurgeons elect management with third ventriculostomy and choroid plexus cauterization, but success is variable and not considered standard of care.
- Orthopedic procedures.
  - Evaluation for clubfeet and casting or splinting before discharge if necessary
    - — Many children relapse after initial management and require soft tissue releases or bony surgical intervention.
    - — Most require orthotics for maintenance of foot position and gait optimization.
  - Pavlik harness if required
  - Prevention of hip flexion contractures and bracing to maximize strength and function

- Hostile bladder or reflux.
  - Clean intermittent catheterization (CIC) program.
  - Many centers recommend CIC for all; others recommend watchful waiting with risk for irreversible renal changes.
  - By 5 years of age, children are able to learn to perform their own catheterizations.
  - Medication can assist with urine storage and help children stay dry.
- Constipation and incontinence.
  - Fiber-rich diet
  - Promotility agents
  - Regular manual removal of stool to help with incontinence
  - Suppository or enema with digital stimulation near internal anal sphincter
  - For those unable to achieve continence, surgery to create a conduit from the abdominal wall to the colon
- Skin care.
  - Parents and children should be taught how to prevent skin breakdown in insensate areas.
    - — Regular checks
    - — Pressure relief exercises
  - 4 stages of skin breakdown according to National Pressure Ulcer Advisory Panel
    1. Intact skin with non-blanching erythema
    2. Skin open with blister or damaged dermis
    3. Subcutaneous involvement
    4. Involvement of muscle, bone, or tendons
  - Pressure ulcer treatment may include
    - — Cleaning and protecting wound
    - — Debridement of dead tissue
    - — Plastic surgery
- Respiratory problems.
  - Stridor and breathing difficulty caused by hydrocephalus and Arnold-Chiari malformation may require urgent intervention.
    - — Shunt or Chiari malformation decompression
  - Severe respiratory dysfunction.
    - — Tracheostomy
    - — Assistive ventilation
- Prevention of obesity and endocrine complications.
  - Aerobic exercise
  - Healthy eating
  - Regular screening for type 2 diabetes
  - Monitor for bone density caused by decreased weight bearing
- Swallowing assessment.
- All children with myelomeningocele are considered latex sensitive; 50% develop latex allergies.
  - Avoid latex in toys, household objects, and medical equipment.
  - Allergy testing and epinephrine autoinjector if latex allergy is suspected.
  - Alert parents to cross-reactivity with bananas, kiwi, and avocado and avoidance in latex-allergic child.
- Physical therapy consultation.
  - Teach family a home program for stretching, positioning, splint management (if needed).
- Referral to early intervention services and community programs.

WHEN TO ADMIT

- When the child is acutely ill and cannot be managed at home
- When there is concern for sepsis or shunt infection
- When the child requires surgical intervention

WHEN TO REFER

- Prenatal discovery of myelomeningocele.
  - Refer mother to a high-risk obstetrics and tertiary medical center specializing in care of neonates with congenital malformations.
- Prenatal diagnosis before 25 weeks, and mother is interested in pursuing fetal repair.
  - Refer to a quaternary medical center with a multidisciplinary team specializing in fetal surgery.
- All neonates born with myelomeningocele.
  - Monitoring by a multidisciplinary team, including experts in psychiatry, child development, neurosurgery, orthopedics, urology, neuropsychology, orthotics, social work, nursing, physical and occupational therapy, and plastic surgery
- Early referral to an ophthalmologist, geneticist, and an early intervention program.
- Parents considering subsequent pregnancies.
  - Refer to genetic counseling.
- Individuals with myelomeningocele who are considering having children
  - Refer to genetic counseling.
  - Refer women to high-risk obstetrics.

FOLLOW-UP

- Primary care in a medical home along with coordinated care in an interdisciplinary spina bifida clinic
  - Aggressive management to prevent secondary conditions and complications
- Meet developmental needs in context of family and community.
  - Accommodations to maximize function despite limitations
  - Adaptive equipment, such as braces and mobility devices
- Consider developmental skills by domain: self-care, mobility, cognition, and social skills.
- Neuropsychological testing to evaluate specific neurocognitive deficits.
- Regular neurologic follow-up with documentation of neurologic function.
- Ongoing monitoring for neurogenic bowel and bladder.
  - Spontaneous voiding does not indicate normal bladder activity.
- Prevention of contracture development at hips, knees, and ankles through maintaining range of motion.

COMPLICATIONS

Vertebral Malformations

- Caused by abnormal segmentation or formation, including
  - Absent vertebrae
  - Partial vertebrae
  - Fused vertebrae
  - Butterfly vertebrae
- Neonates may be born with or develop
  - Kyphosis.
  - Lordosis.
  - Scoliosis.
  - Neuromuscular scoliosis.
  - Nearly 90% with lesions above the sacral level have kyphosis, scoliosis, or both.
    - — May lead to cardiac restriction, pain, skin breakdown, spinal cord damage

Spinal Cord Malformation

- Results in
  - Loss of sensation, making child vulnerable to skin breakdown, burns, abrasions
  - Loss of motor function
- Loss of motor function leads to decreased movement in utero.
  - Resulting in deformities seen at birth, such as clubfoot, dislocated hips
- Developmental milestones.
  - Delay of gross motor skills, ambulation.
  - Association between limited mobility and development of visual perceptual skills.
  - Quadriceps strength is a major predictor of community and household ambulation.
- Intestines.
  - Neurogenic bowel characterized by constipation and fecal incontinence
- Urinary system.
  - Neurogenic bladder (neurogenic voiding dysfunction).
  - Reflux and hydronephrosis may lead to permanent kidney damage.
- Male reproductive system.
  - Erectile dysfunction or impaired ejaculation.
  - Decreased fertility.
  - One study found only 35% of men reported successful sexual intercourse.
- Female reproductive system.
  - Decreased sensation and lubrication (although many can achieve orgasm)
  - Normal fertility
- Tethered cord symptoms include
  - Change in bladder habits, repeated urinary tract infections, upper tract dilation, vesicoureteral reflux.
  - Worsening weakness and foot deformities, changes in lower extremity tone.
  - Surgical untethering procedure is straightforward but many require re-tethering because of scar tissue or preexisting anatomic abnormalities.

Spinal Curvature

- Most are born with or develop scoliosis or kyphosis as they age.
- Curvature development is correlated with presence of congenital vertebral abnormalities, such as
  - Hemivertebrae or wedge vertebrae
  - Higher lesion level and higher motor level
- Rapidly progressive curves should prompt evaluation for syringomyelia or tethered cord.
  - Neurologic function may require neurosurgical intervention before orthopedic intervention.
- Goals in managing curvature include
  - Preventing progression of deformity
  - Achieving solid fusion with level pelvis for sitting tolerance
  - Functional independence

- Operative indications are not clear cut.
  - For many surgeons, scoliosis >50° is indication for surgery.
  - Grow rods or vertebral expandable prosthetic titanium rib procedure have been used to preserve growth.
  - Surgical risks include infection, skin breakdown, loss of functional skills, loss of sensation or motor control, and pseudarthrosis.
  - Physical and occupational therapy to assist with adaptations and safe transfers.
  - Activity restrictions followed by therapy to restore function.

Arnold-Chiari Malformation

- Brain stem and part of the cerebellum are displaced downward.
- Brain stem and proximal spinal cord compression can lead to
  - Difficulty swallowing, choking
  - Hoarseness
  - Central apnea, disordered breathing
  - Opisthotonos
  - Cranial nerve dysfunction
  - Sudden death
- New-onset Arnold-Chiari malformation should be evaluated for worsening hydrocephalus and syringomyelia.

Hydrocephalus and Shunt Malfunction

- Sudden shunt malfunction may produce life-threatening elevations of intracranial pressure, requiring emergency intervention.
  - Signs and symptoms of acute shunt malfunction include
    - Bulging fontanel
    - Exceeding normal head circumference
    - Sixth nerve palsy
    - Sunsetting eyes
    - Paralysis of upward gaze
    - Vomiting
    - Headache
    - Irritability
    - Lethargy
  - Progression may rapidly ensue to
    - Loss of consciousness
    - Abnormal pupillary reflexes
    - Deterioration to death
- Symptomatic hydrocephalus is an indication for urgent evaluation by a neurosurgeon.

Other Intracranial Abnormalities

- Partial dysgenesis of corpus callosum
- Cortical dysplasias
- Abnormal cortical thickening in frontal regions
- Reduced cortical thickness in posterior regions
- Reduced cerebellar size
- Limbic track anomalies
- Seizures

Respiratory Dysfunction

- Hydrocephalus and Arnold-Chiari malformation can cause
  - Vocal cord paralysis
  - Central hypoventilation
  - In severe cases: stridor, increased work of breathing, apnea
- Restrictive lung disease from poor chest wall compliance, made worse by progressive scoliosis
- Sleep exacerbated respiratory dysfunction

Endocrine Abnormalities

- Risk for obesity increased for nonambulatory children with higher lesion levels
- Increased risk for type 2 diabetes
- Increased risk for precocious puberty in girls

Intellectual Impairment

- Three-fourths of children with myelomeningocele have normal IQs.
- Intellectual impairment is more frequent with higher level lesions and brain malformations.
- Those without hydrocephalus tend to have higher IQs and better executive function and memory.

Psychosocial Complications

- Barriers to independent functioning.
- Higher than average rates of depression and anxiety.
- Family may experience substantial social and financial pressures.

PROGNOSIS

- Survival rate and functional outcomes have improved over the past 50 years.
- Except for children with very high lesions, motivated children can walk.
  - Those with high lumbar and lower thoracic lesions may require extensive bracing, assistive devices, or intense physical therapy.
  - With low lumbar or sacral lesions assistive devices may not be required for ambulation.

- Risk for death is 10-fold higher than the general population for 5- to 40-year-olds with myelomeningocele.
  - Most deaths are unexpected.

PREVENTION

- Folic acid supplementation decreases risk of myelomeningocele.
  - American Academy of Pediatrics and Centers for Disease Control and Prevention recommend
    - 0.4-mg folic acid daily for all women of childbearing age
    - 4 mg of folic acid daily for women with neural tube defects or first-degree relatives with neural tube defects
- Prenatal surgery.
  - Major risks of this procedure include preterm delivery and maternal complications (bleeding and infection).

DEFINITION

- *Scoliosis* is a side-to-side curve of the spine, usually idiopathic.
  - Traditionally classified as
    - — Infantile (0–3 years)
    - — Juvenile (4–10 years)
    - — Adolescent (>10 years)
  - The term *early-onset scoliosis* is used for onset of deformity <5 years.
  - Adolescent idiopathic scoliosis is the most common form of acquired scoliosis.
- *Spina bifida* (myelomeningocele) refers to failure of formation of posterior neural arch, of the dural layers, and overlying skin.
- *Larsen syndrome* is an autosomal-dominant osteochondrodysplasia.
- *Dysraphism* is failure of closure of the primary neural tube.
- *Kyphosis* is an acquired dorsal hump.
- *Spondylolysis* is a defect in the continuity of the pars interarticularis of the posterior portion of L4 or L5.
- *Spondylolisthesis* is a forward slippage of one vertebra on the vertebra below.
- Infections of the spine (pyogenic spondylitis).
  - Includes diskitis and vertebral osteomyelitis.
  - Both entities may represent different points on the spectrum of the same process.

SIGNS AND SYMPTOMS

Postural

- Back pain in children may be a sign of an underlying disorder.
- Postural abnormalities may or may not indicate an underlying spine disorder.
- The challenge to the physician is to determine whether the child's posture is caused by
  - Underlying skeletal deformity
  - A habit that has altered—exaggerates, increases, or decreases—normal spinal curves
- Abnormal curvatures and protrusions merit careful investigation.
- Thoracic spine normally has some kyphosis.
- Cervical and lumbar spine normally have slight lordosis.
- If either condition is excessive, progressive, or painful, concern is appropriate.
- Scoliosis is always abnormal.

Congenital Malformations

- When the newborn is held prone in the examiner's palm, the newborn's back falls into slight flexion, allowing detection of
  - Meningomyelocele
  - Scoliosis
  - Kyphosis
  - Dorsolumbar hyperflexion
- Lumbar spinal deformity may be indicated by
  - Hair tuft
  - Dimple
  - Discoloration
  - Palpable spina bifida lamina defect

Congenital Scoliosis

- Vertebral anomalies are present at birth.
- Clinical deformity develops with spinal growth.
  - May not become apparent until later childhood
  - Sometimes related to cardiac or urologic abnormalities

Congenital Kyphosis

- More severe deformities are usually recognized in the neonate.
  - Rapidly progress thereafter
- Less obvious deformities may not appear until several years later.

Spina Bifida

- Spina bifida can be mild and of no clinical significance (occulta).
- Can be severe (vera), with meningeal protrusion (meningocele) or protrusion of both meninges and neural elements (myelomeningocele) posteriorly.
  - When the protrusion includes bony elements, it may transfix the spinal cord.
  - Transfixing spur is called *diastematomyelia.*
  - Most of the lesions occur in the lower lumbar and upper sacral areas.
  - Few spinal defects are at a higher level.

Larsen Syndrome

- Characteristic pattern of spinal deformity consisting of
  - Vertebral anomalies
  - Spondylolysis
  - Scoliosis (seen in 25%–70%)
- Cervical spine is the most severely involved.
- Patients have very marked orthopedic-related problems, including
  - Multiple dislocated joints
  - Clubfeet
  - Cervical kyphosis
  - Scoliosis

- Most consistent patterns of deformity represented by
  - Dysraphism
  - Hypoplasia

Goldenhar Syndrome (Oculoauriculovertebral Dysplasia)

- Abnormalities include
  - Ocular
  - Auricular
  - Vertebral
- Wide phenotypic variation.
- The spectrum includes ≥2 of the following abnormalities:
  - Ear malformations (including microtia and accessory tragi)
    - Multiple accessory tragi in a preauricular mandibular distribution is common and an important diagnostic clue.
  - Low-set ears
  - Hemifacial microsomia (including micrognathia)
  - Coloboma
  - Fused or cervical hemivertebrae
- Multiple malformations, including congenital heart, brain, and renal disease, seen in small numbers of patients.
- Spinal abnormalities present in ≤60%.
  - Congenital malformations as seen in patients with congenital scoliosis are common.

Morquio Syndrome (Mucopolysaccharidosis [MPS] type IV)—Odontoid Dysplasia With Atlantoaxial Subluxation

- The disorder consists of 2 forms with similar clinical findings and autosomal-recessive inheritance.
  - MPS IV-A
  - MPS IV-B
- In both forms, mental symptoms are absent or only mildly present.
- Neurologic symptoms may result from compression of spinal cord or medulla.
- These children seem typical at birth but will present at 12–18 months of age with an atypical appearance.
- Musculoskeletal findings may include
  - Joint laxity
  - Short stature
  - Pectus carinatum
  - Genu valgum
  - Pes planus
  - Enlarged joints
  - Short neck
- Corneal clouding is present in 50% of cases.
- These individuals often stand with hips and knees flexed, head thrust forward.

VACTERL Association

- The categorical breakdown of anomalies in a large series was as follows:
  - Vertebral (25%)
  - Anal, esophageal (or other gastrointestinal) atresia (15%)
  - Cardiac (33%)
  - Tracheoesophageal fistula (95%)
  - Urinary (renal dysplasia, urethral valves) (17%)
  - Skeletal (16%)

Acquired Abnormalities

Juvenile Idiopathic Scoliosis

- Presents in the 4- to 9-year-old age group during a time of relatively slow spinal growth

Adolescent Idiopathic Scoliosis

- Usually painless and discovered on routine physical examinations or at school scoliosis screening programs.
  - Typically discovered when truncal asymmetry is noted.
  - Incidence of pain in children with idiopathic scoliosis is no different than in the general population.
    - ~30% report back pain at some time.
  - Pain
    - May arise during a phase of rapid progression of scoliosis
    - Might be related to underlying neurologic disorder
  - The physician should be concerned about pain that arouses the child from sleep.
    - Unlike usually benign pain that delays falling asleep
  - Constant pain is reason for concern.
- Adolescent idiopathic scoliosis is a diagnosis of exclusion.
- The presence of any of the following findings should be noted:
  - Abnormal cutaneous findings.
  - Asymmetry of shoulder height and scapular prominence.
  - Waistline asymmetry.
  - Iliac crest height discrepancy, indicating a leg-length discrepancy.
  - The patient's feet should be assessed for asymmetry or deformity.
- A complete neurologic examination should be done.

- Adam forward bend test is commonly used to assess the rib or flank prominence created by scoliosis.
- A scoliometer measurement can be made of the angle of trunk rotation (ATR).
  - A 7° ATR is often cited as the magnitude at which to initiate referral.

Kyphosis

- The most common site is the lower thoracic vertebrae.
  - Can occur in any site in the vertebral column
- The initial event is bulging of intervertebral disks in direction of contiguous vertebral bodies.
  - Exerts pressure against cartilage plates
  - Causes thinning of plates
- Interferes with endochondral bone formation on the growth surface of plates.
  - Causes gaps that are basis for herniation of disk into the bodies
  - Isolates apophyseal ossification center from vertebral body
- Disk space narrows, more so anteriorly.
  - Causes increased pressure on anterior portions of contiguous vertebral bodies
  - Impedes their longitudinal growth anteriorly
  - Results in attendant kyphosis
- An aching pain aggravated by physical exertion is present in the affected part of the vertebral column in children with Scheuermann disease.
  - The affected area is tender to palpation.
  - Having the patient assume a stooping position often causes increased pain.
- In many instances, pain is so minor that the patient first complains to the physician about pain caused by poor posture; then kyphosis is noted.
- In some children, the condition can progress to cause severe deformity and dysfunction.

Spondylolysis and Spondylolisthesis

- The diagnosis is usually suggested by history and physical examination findings and confirmed with radiographs.
- Horizontal slippage can occur anywhere in the vertebral column.
  - Usually involves the L5 vertebral body moving anteriorly in relationship to S1
- Spondylolysis and spondylolisthesis can cause back pain, which
  - May radiate to the buttocks, although true radicular symptoms are rare
  - Usually is activity related
  - Is worse when upright than when seated or supine
- Spondylolysis often causes back pain before spondylolisthesis develops.
  - Flattening of normal lumbar lordosis with posterior tilting of pelvis is noted in spondylolysis.
  - Defect in the arch dissociates vertebra from its inferior facet and posterior ligamentous restraints.
    - Separation may allow slow forward slippage of vertebra on the vertebra below.
- Low back pain is the most common symptom.
- Some cases are diagnosed because the patient has
  - Abnormal gait
  - Postural deformity
- Only 10%–15% of patients ever develop symptoms.
- Spondylolisthesis can progress in certain children, especially during times of accelerated growth.
  - In children ≤10 years, periodic follow-up is recommended.
  - The physical examination may reveal
    - Tenderness in the lower back
    - Tight hamstrings
    - In the case of a high-grade slip (>50%), forward-leaning posture with the hips and knees flexed
  - Usually, patients experience pain with trunk extension.

Infections of the Spine

- Children >8 years occasionally have staphylococcal infections of the spine.
- Affected patients
  - May present with abdominal pain, back pain, limp, or refusal to walk.
  - May seem ill.
  - Typically try to avoid flexion of the spine and have a very hard time picking objects up off the floor.
  - Typically flex through their knees and avoid flexing the trunk.

DIFFERENTIAL DIAGNOSIS

Classification of Spinal Deformity

- Idiopathic
  - Infantile
  - Juvenile
  - Adolescent

- Neuromuscular
  - Neuropathic
    - Upper motor neuron lesions
      - Cerebral palsy
      - Spinocerebellar degenerations
      - Syringomyelia
      - Spinal cord tumor
      - Spinal cord trauma
    - Lower motor neuron lesion
      - Poliomyelitis
      - Other viral myelitis
      - Trauma
      - Spinal muscular atrophy
      - Myelomeningocele (paralytic)
    - Dysautonomia (Riley-Day syndrome)
  - Myopathic
    - Arthrogryposis
    - Muscular dystrophy
    - Fiber-type disproportion
    - Congenital hypotonia
    - Myotonia dystrophica
- Congenital
  - Congenital scoliosis
    - Failure of formation
    - Wedge
    - Hemivertebra
    - Failure of segmentation
      - Unilateral bar
      - Bilateral bar
  - Congenital kyphosis
    - Failure of formation
    - Failure of segmentation
    - Mixed
  - Congenital lordosis
  - Associated with neural tissue defect
    - Myelomeningocele
    - Meningocele
    - Spinal dysraphism (diastematomyelia)
- Neurofibromatosis
- Mesenchymal
  - Marfan syndrome
  - Ehlers-Danlos syndrome
- Traumatic
  - Fracture or dislocation
  - After irradiation
  - After laminectomy
- Soft-tissue contractures
  - After thoracoplasty
  - Burns
- Osteochondrodystrophies
  - Achondroplasias
  - Spondyloepiphyseal dysplasia
  - Diastrophic dwarfism
  - MPS
- Scheuermann disease
- Infection
- Tumor
- Rheumatoid disease
- Metabolic
  - Rickets
  - Juvenile osteoporosis
  - Osteogenesis imperfecta
- Lumbosacral anomalies
- Hysterical
- Functional
  - Postural
  - Secondary to short limb
  - Secondary to pain

DIAGNOSTIC APPROACH

Congenital Malformations

Goldenhar Syndrome (Oculoauriculovertebral Dysplasia)

- No clear standard for diagnosis
- Authorities generally agree that the spectrum includes ≥2 of the following abnormalities:
  - Ear malformations
    - Including microtia and accessory tragi
  - Low-set ears, hemifacial microsomia
    - Including micrognathia
  - Coloboma
  - Vertebral anomalies
    - Fused or cervical hemivertebrae
- Multiple accessory tragi in a preauricular-mandibular distribution
  - One of the more constant findings
  - Important diagnostic clue to recognizing the syndrome

Acquired Abnormalities

Adolescent Idiopathic Scoliosis

- Discovered at
  - Routine physical examinations
  - School scoliosis screening programs
- Perform an Adam forward-bend test to screen for scoliosis.
  - Child bends forward until
    - Spine is horizontal with the neck relaxed.
    - Knees fully extended.
    - Feet together.

  - Upper limbs dependent.
  - Palms opposed.
- When the patient bends forward, the site and direction of the scoliosis are indicated by prominence of
  - One scapula
  - One side of the rib cage
  - Lumbar paraspinous muscles
- Truncal rotation (prominence) may be quantified with inclinometer or scoliometer.
  - Center over the apical spinous process (at the maximal degree of rotation and prominence).
- 7° of rotation corresponds with 20° of coronal deviation.

LABORATORY FINDINGS

- Infections of the spine
  - Inflammatory markers, such as C-reactive protein and erythrocyte sedimentation rate, are commonly elevated.

IMAGING

- Infantile idiopathic scoliosis
  - Rib vertebral angle difference is defined as the difference in angulation of left and right ribs on apical vertebra as measured on an anteroposterior radiograph.
  - Children with curves >20° should have total spine magnetic resonance imaging (MRI) to rule out an underlying dysraphism.
- Juvenile idiopathic scoliosis
  - Total spine MRI to rule out an underlying spinal dysraphism
- Adolescent idiopathic scoliosis
  - Standard screening radiographs include upright posteroanterior and lateral views that include cervical spine and pelvis.
    - Lateral radiograph should be taken with elbows flexed in front of the patient and hands positioned beneath the chin.
    - Curves are measured with the Cobb measurement.
  - MRI or computed tomography (CT) if an underlying neural axis or structural abnormality is suggested by history, physical examination, or radiographs.
    - Suggestive radiographic findings include
      - Convex left thoracic curves
      - Double thoracic curves
      - Triple curves
      - Long right thoracic curves with an end vertebra (the last vertebra contributing to the Cobb measurement) caudal to T10
      - Curves with a high or low apex
    - Thoracic curves with normal kyphosis or hyperkyphosis on lateral radiograph should raise suspicion of underlying neural axis abnormality.
  - A bone age radiograph (posteroanterior left hand radiograph) to discover whether patient's chronologic age and skeletal age differ.
  - Lateral radiograph of the elbow to determine whether patient has achieved peak height velocity.
- Larsen syndrome, if cervical kyphosis is present
  - MRI to evaluate for cord compression
  - CT to evaluate for anteroposterior dissociation
- Morquio syndrome
  - Radiography reveals flattened vertebrae with an anterior beak in the thoracolumbar spine.
  - Flexion-extension cervical spine radiographs to evaluate for atlantoaxial instability secondary to odontoid hypoplasia.
- Kyphosis
  - Radiography
    - Reveals narrowing of anterior disk space and defects on surfaces of adjacent vertebrae at sites where disk tissue has penetrated vertebral bodies
    - Schmorl nodule: prolapsed disk tissue that, in time, becomes walled off by osseous tissue and forms a bulbous mass of extruded tissue appearing as area of lucency in the affected body
- Spondylolysis and spondylolisthesis
  - Single-photon emission CT is useful when the diagnosis is suspected but radiographs are normal.
  - Oblique radiography reveals the pars interventricularis defect.
  - Standing lateral radiography demonstrates spondylolisthesis.
  - CT is useful for gaining a better assessment of bony detail.
  - MRI is useful when neurologic symptoms are present.
- Infections of the spine
  - Radiograph reveals disk space narrowing and end plate irregularities.
  - MRI further delineates the extent of disease and reveals any abscesses.

TREATMENT APPROACH

- Treatment options depend on patient's overall health, degree of truncal deformity, effect of spinal deformity on patient function, and caregiver's expectations.
- The effect of bracing is controversial; however, it can improve the patient's sitting balance.
- Several groups have reported exciting advances in spinal surgery to correct acquired and congenital deformities.
  - Surgical intervention is sometimes warranted when scoliosis is causing severe restrictive lung disease.
  - Spinal fusion and instrumentation may be necessary for progressive curves causing functional limitations, particularly with wheelchair sitting.
    - Usually involves fusion to the sacrum with fixation to the pelvis to control pelvic obliquity
    - Extensive operation with significant risks but with reports of very high caregiver satisfaction
- Growing rods.
  - Revived technique.
  - Research is showing it is a viable option for preserving near-normal growth of the spine in congenital and acquired disorders.
- New techniques have been described recently, including
  - Vertebral stapling that produces asymmetric and corrective growth of the concavity of a deformity
  - Vertical expandable prosthetic titanium rib instrumentation
    - Indirectly corrects spine deformity
    - Protects spine growth remaining to treat an associated thoracic insufficiency syndrome
- Wheelchair modification can be effective.

SPECIFIC TREATMENTS

Congenital Malformations

Congenital Scoliosis

- Management requires frequent clinical and radiographic follow-up to detect progression.
- When located near the middle of the spine
  - Segments of spine above and below compensate by curving in opposite directions.
  - The result is a balanced spine and a straight back.
  - Treatment is unnecessary.
- When asymmetric vertebra is at the base of the spine (lumbar, sacral, or lumbosacral)
  - The compensatory curve that develops above is insufficient.
  - Curvature progresses as the patient grows.
  - Many surgeons now advocate excision of the anomalous vertebra and a short segment fusion to prevent progression.
- When deformity occurs in the upper thoracic spine or cervicothoracic junction
  - It does not typically cause large curves.
  - However, it can elevate the shoulder on the convex side of the curve and cause an oblique takeoff of the cervical base, resulting in head tilt.
    - Causes significant cosmetic concern
  - For progressive deformities, treatment can involve many different strategies, depending on
    - Type of anomaly (isolated or diffuse)
    - Location and degree of the deformity
    - Age of the patient
  - Emphasis currently is placed on treatment methods that avoid early or extensive spinal fusion to gain additional chest wall growth and pulmonary development in these often young patients.
  - For thoracic insufficiency syndrome
    - The vertical expandable prosthetic titanium rib
      - Can be anchored to the ribs, spine, and/or pelvis to simultaneously expand the chest wall and control spine deformity.
      - The device usually is lengthened every 6 months.
      - Use has gained in popularity as an alternative to early spinal fusion.

Congenital Kyphosis

- When necessary, the treatment is fusion.

Larsen Syndrome

- Surgical treatment of cervical kyphosis if the spinal cord is under compression
  - Posterior spinal fusion if cord compression is evident by imaging or physical examination.
  - Continued anterior spinal growth may correct the deformity with time.
- Long anteroposterior fusion if anteroposterior dissociation is present

Morquio Syndrome (MPS Type IV)—Odontoid Dysplasia With Atlantoaxial Subluxation

- Surgery to stabilize upper cervical spine.
  - Perform before development of cervical myelopathy.
  - Use posterior spinal fusion.
  - Can be lifesaving.
- Surgical intervention for atlantoaxial instability secondary to odontoid hypoplasia.
- Surgical neural element decompression and spinal fusion may be required for thoracolumbar kyphosis that does not resolve with growth.

Acquired Abnormalities

Infantile Idiopathic Scoliosis

- Treatment is difficult because of the young age of the patients.
- Early spinal fusion should be avoided to allow for continued chest wall and lung development.
- Bracing does not seem to affect the natural history of the disease.
- Serial casting has recently gained momentum with some reports of controlling the deformity.
- If resolution is not accomplished or the deformity continues to progress, surgical options that do not involve a formal fusion of the spine should be considered.

Juvenile Idiopathic Scoliosis

- Treatment depends on patient age and degree of progression.
- Patients with curves ≥30° at the onset of puberty have a 100% chance of requiring surgery.
- Bracing
  - Can be instituted for curves >20°–25°
  - Can be attempted for larger curves in hopes of slowing progression to allow chest wall development
- Surgical treatment can be considered in a skeletally immature patient with a curve >40°.
  - Non-fusion instrumentation (growing rods) recently have been emphasized.
    - — Controls the deformity but still allows growth.
    - — Definitive spinal fusion and instrumentation can be postponed to allow adequate chest wall and pulmonary development.

Adolescent Idiopathic Scoliosis

- Treatment is undertaken to prevent sequelae of untreated severe scoliosis.
  - Pulmonary restriction
  - Significant back pain
  - Cosmetic deformity
- Exercises are of no benefit in slowing or reversing progress of scoliosis.
- Treatment depends on child's age and the curve magnitude.
- Bracing.
  - Usually initiated in skeletally immature patients (Risser grades 0–2)
    - — With 30°–45° curve *or*
    - — With curve that has progressed >5° after presenting at 25°–30°
  - Considered for Risser grade 0 with curve ≥25°.
- Surgery.
  - Considered for curves that continue to progress >50° in the thoracic spine and ~40°–45° in the thoracolumbar or lumbar spine.
    - — The goal is to balance the trunk, while fusing the fewest levels possible and obtaining a solid fusion to prevent progression.
  - Posterior spinal fusion and instrumentation is most common.

Kyphosis

- Treatment is aimed at preventing further deformity by casting or bracing.
- Treatment depends on the cause of the hyperkyphosis.
  - In medically related problems, the underlying problem has to be addressed.
  - Surgical stabilization is required for compromise secondary to previous operation, tumor treatment, infection treatment, or trauma.
- For patients with maintained spinal stability and acceptable balance, casting or bracing may assist with pain management until the underlying problem has been addressed.
- In children with Scheuermann disease
  - The natural history is generally benign.
  - Indications for the surgical treatment are limited.
  - Bracing may be useful in children who have adequate growth remaining.
  - Physical therapy focusing on spinal extensor and abdominal wall strengthening should be attempted for ≥6 months before surgical treatment is considered.
- Surgery may be necessary for kyphosis >70°.
  - For patients who have recalcitrant pain
  - For patients with a self-perceived unacceptable appearance
- Surgery most commonly involves an instrumented fusion procedure.

Spondylolysis and Spondylolisthesis

- In the absence of symptoms, spondylolysis or spondylolisthesis with <50% listhesis requires no treatment.
- Treatment is typically aimed at alleviation of back pain.
  - For significant low back pain, activity modification, physical therapy, and bracing to ameliorate symptoms.
  - For recalcitrant pain or pain associated with slips >50%, surgical stabilization may be necessary.
- In spondylolysis in an otherwise normal spine
  - Pars interarticularis repair can be attempted to preserve motion.
    - Defect is treated like a fracture, avoiding a formal spinal fusion.
- For spondylolisthesis, particularly listhesis >50%
  - Surgical stabilization, usually with instrumented spinal fusion.
  - Whether the listhesis should be reduced or whether the surgery is performed anteriorly, posteriorly, or by a combined approach is still under debate.

Infections of the Spine

- Treatment is generally nonsurgical.
- Antibiotic treatment targeted for *Staphylococcus aureus* is usually curative.
- An orthosis may be used to treat pain.
- Infectious disease consultation may be appropriate.
- For those who do not respond, an image-guided percutaneous biopsy can be performed.
- Atypical infections must be considered.
  - Tuberculosis of the spine (Pott disease) typically affects the vertebral body to a greater extent and can spread subligamentously (beneath the anterior longitudinal ligament).

WHEN TO REFER

- Scoliosis
  - Referral to a spine specialist is recommended in congenital scoliosis.
  - Refer to a pulmonologist if there are concerns for restrictive lung disease.
- Adolescent idiopathic scoliosis
  - Refer to a pediatric orthopedist when 7° of rotation corresponds with 20° of coronal deviation.
- Morquio syndrome
  - Referral to a pulmonologist for pulmonary complications, such as obstructive sleep apnea and restrictive lung disease

COMPLICATIONS

Congenital Malformations

- Congenital scoliosis
  - A certain subset of patients with congenital scoliosis can develop deformities that lead to *thoracic insufficiency syndrome*.
    - Inability of the thorax to support respiration or lung growth.
    - The classic description is that of a patient with fused or absent ribs on the concave side of the deformed spine.
    - Ultimately leads to restrictive lung disease and eventual cardiopulmonary failure.
- Congenital kyphosis
  - Progressive deformity in the thoracic spine can result in paraplegia.
  - Severe cases can lead to restrictive lung disease and respiratory symptoms, such as dyspnea.
- Larsen syndrome
  - Cervical kyphosis and anteroposterior dissociation must be considered during intubation for required surgical procedures.
  - Bracing for scoliosis may cause chest wall deformities.
- Morquio syndrome (MPS type IV)—odontoid dysplasia with atlantoaxial subluxation
  - Atlantoaxial instability secondary to odontoid hypoplasia can cause upper cervical cord compression.
    - Insidious onset of cervical cord compression may cause fatigue progressing to weakness.

Acquired Abnormalities

- Infantile idiopathic scoliosis
  - Most of these curves are self-limiting.
  - Those that progress can be difficult to manage.
    - Usually double structural curves
  - In cases in which the rib vertebral angle difference is >20°, progression is likely.

PROGNOSIS

Congenital Malformations

- Congenital scoliosis
  - Life expectancy can be reduced significantly in infantile idiopathic scoliosis by cardiopulmonary compromise.
  - Overall, this disorder shows progression in 75% of cases.
    - Curve progression is strongly related to the type of vertebral anomaly.

- The poorest prognosis is for unilateral unsegmented bars with contralateral hemivertebrae.
  - Up to 10° per year progression
- Curves tend to progress if they exceed 40°–50° before skeletal maturity.
- Less severe progression in cases of
  - Unilateral unsegmented bar (5°/y)
  - 2 unilateral fully segmented hemivertebrae (3°/y)
  - Unilateral fully segmented hemivertebra (1°–2°/y)
- Least severe progression in patients with block and wedge vertebrae.

- Congenital kyphosis
  - After progression begins, it does not cease until end of growth.
- Juvenile idiopathic scoliosis
  - Often progressive.
    - Estimated at ~70%
  - Potential for trunk deformity with cardiac and pulmonary compromise exists.
    - Especially in scoliosis with onset <5 years
  - Curves >30° are almost always progressive.
    - Rate of 1°–3° per year <10 years
    - Rate of 4.5°–11° per year >10 years

Acquired Abnormalities

- Adolescent idiopathic scoliosis
  - 5% of those with disease have a progression of the curve to >30°.
    - Progression of scoliosis is dependent on
      - Growth velocity
      - Magnitude of the curve at first visit
    - Progression is most notable with a growth velocity of >2 cm per year.
      - Between 9 and 13 years
      - At bone ages between 9 and 14 years
      - Between 0.5 and 2 years before menarche
    - Main progression occurs at the time of most rapid skeletal growth.
      - 11–13 years for girls
      - 13–15 years for boys
    - Primary thoracic curve scoliosis progresses more than primary lumbar curve scoliosis.
- Kyphosis
  - In some children, the condition can progress to cause severe deformity and dysfunction.
  - In others, it stabilizes and the deformity may disappear.
- Spondylolysis and spondylolisthesis
  - Progression is estimated to occur in 5%–7% of patients with spondylolisthesis.
    - Most likely to occur during the adolescent growth spurt

PREVENTION

- The efficacy of school screening remains controversial.

DEFINITION

- *Splenomegaly* is enlargement of the spleen resulting from abnormalities of its lymphoid, reticuloendothelial, or vascular components.

HISTORY

- In most cases, the cause of splenomegaly can be determined by history and physical examination.
- Travel and family history may be relevant.
- In infants, ask about birth history and the early neonatal period.
  - A history of umbilical vein catheterization or omphalitis in the neonatal period may suggest a diagnosis of portal vein thrombosis.
- In a newborn with unexplained jaundice, consider congenital hemolytic anemia, especially if there is a family history of
  - Anemia
  - Jaundice
  - Splenomegaly
  - Splenectomy
- A viral cause (eg, Epstein-Barr virus, cytomegalovirus) should be considered in a child with a history of
  - Fever
  - Pharyngitis
  - Malaise
- Malaria or histoplasmosis may be the cause if the patient has recently traveled to areas endemic for these diseases.
- An underlying inflammatory, infectious, or malignant process should be suspected in the patient with
  - Fever
  - Night sweats
  - Malaise
  - Weight loss
  - Rash
  - Arthralgia
  - Bone pain

PHYSICAL EXAMINATION

- Spleen length is correlated with age, height, weight, and body surface area in a nonlinear fashion, similar to the liver.
  - Size is recorded as centimeters below the costal margin in the midclavicular and anterior axillary lines.
  - Measure this span with a rigid ruler.
- Wide interobserver variability exists in the ability to detect an enlarged spleen on examination.
  - Not generally associated with clinical experience
- The spleen
  - Moves downward with inspiration
  - Enlarges diagonally across the midline toward the right iliac fossa
- A palpable spleen may be normal.
  - Can be the result of thin abdominal musculature.
  - However, the concomitant finding of hepatomegaly is usually pathologic, warranting further investigation.
- An enlarged spleen may extend into the pelvis.
- Palpation and percussion are important techniques in the physical examination of the child with suspected splenomegaly.
  - Palpation
    - Begin in the right lower quadrant.
    - Move across the abdomen toward the left upper quadrant.
    - The normal palpable spleen is
      - Soft
      - Smooth
      - Nontender
      - <1–2 cm below the left costal margin
    - A pathologically enlarged spleen
      - Is usually firm
      - Has an abnormal surface
      - Is often associated with signs and symptoms of an underlying disease
    - Spleen may be tender if it has enlarged quickly.
      - Splenic sequestration
      - Splenic trauma with subcapsular hemorrhage
    - When portal hypertension causes splenomegaly, dilation of the superficial abdominal veins can be seen.
- Percussion.
  - Percussion cannot confirm splenic enlargement but can raise suspicion.
  - An enlarged spleen replaces the tympany of the stomach and colon with the dullness of a solid organ.
  - If tympany is prominent, especially laterally, splenomegaly is not likely.
  - A change from tympany to dullness on inspiration when percussing at the lower interspace in the left anterior axillary line suggests splenic enlargement.
- Consider an autoimmune disorder when splenomegaly is accompanied by
  - Rash
  - Arthritis
  - Mucosal ulcerations

DIFFERENTIAL DIAGNOSIS

Infections

- Viral infection
  - The most common cause of splenomegaly in children.
  - Splenic enlargement is usually transient and mild to moderate in severity.
  - Common viral infections include
    - Epstein-Barr virus (infectious mononucleosis)
      - Splenomegaly occurs in 50%–75% of cases of infectious mononucleosis.
    - Cytomegalovirus
    - HIV
- Bacterial infection
  - Acute bacterial infections.
  - Subacute bacterial endocarditis.
  - Congenital syphilis.
  - Tuberculosis.
  - Other chronic bacterial infections.
  - Septicemia from meningococcus or pneumococcus may also be associated with splenomegaly.
- Parasitic infection
  - Toxoplasmosis
  - Malaria
  - Leishmaniasis
- Fungal infection
  - Candidiasis
  - Histoplasmosis
    - Progressive disseminated histoplasmosis can occur in healthy children <2 years.
    - Results from exposure to the fungus in endemic areas of the United States (Mississippi, Ohio, and Missouri river valleys).
    - Early symptoms are fever, failure to thrive, and hepatosplenomegaly.
  - Coccidioidomycosis

Hematologic Disorders

- Extramedullary hematopoiesis
  - Occurs in diseases where bone marrow cannot meet need for cell production
    - Thalassemia major
    - Osteopetrosis
    - Myelofibrosis
- Acute splenic sequestration crisis with sickle cell disease
  - A medical emergency that requires prompt recognition and treatment
  - A leading cause of death in children with sickle cell disease
  - A rapidly enlarging spleen with
    - Falling hematocrit
    - Pallor
    - Dyspnea
    - Weakness
    - Left-sided abdominal pain
- Hemolytic anemias—congenital and acquired
  - Red cell membrane defects
    - Hereditary spherocytosis
    - Hereditary elliptocytosis
  - Red cell hemoglobin disorders
    - Sickle cell disease and related syndromes
    - Thalassemia
  - Red cell enzyme defects
    - Glucose-6-phosphate dehydrogenase deficiency
    - Pyruvate kinase deficiency
  - Autoimmune hemolytic anemia

Infiltrative Disorders

- The spleen is commonly enlarged in
  - Untreated leukemias and lymphomas, including Hodgkin disease
  - Lipidoses
  - Mucopolysaccharidosis
    - Phagocytic reticuloendothelial elements of the spleen accumulate large amounts of lipid and mucopolysaccharide, respectively.
  - Langerhans cell histiocytosis
- With malignant infiltration, the spleen is often
  - Firm
  - Massively enlarged
  - Crosses the midline

Congestive Splenomegaly (Banti Disease)

- Splenomegaly may occur from obstruction of the hepatic, portal, or splenic veins.
- Common causes include
  - Portal vein thrombosis.
  - Cirrhosis.
  - Congestive heart failure.
  - Umbilical vein catheterization or septic omphalitis in neonates may obliterate the portal, hepatic, or splenic veins.
- Congestive splenomegaly is the most common cause of "hypersplenism."
  - Splenomegaly
  - Peripheral blood cytopenias from excessive splenic function
  - Increased bone marrow production of the affected blood cells

Inflammatory Diseases

- Splenomegaly can result from increased numbers of reticuloendothelial cells that remove antibody-coated cells and proteins in
  - Systemic lupus erythematosus
  - Juvenile idiopathic arthritis
  - Serum sickness
  - Sarcoidosis
  - Immune thrombocytopenia and neutropenia
- Lymphoid hyperplasia may occur as a result of accelerated antibody production in the spleen.

Primary Splenic Disorders

- Splenoptosis (wandering spleen).
  - A congenital fusion anomaly of dorsal mesogastrium.
  - Results in a spleen of normal size that moves freely within the peritoneal cavity.
  - A patient with splenoptosis usually has an asymptomatic abdominal mass.
- Cysts.
  - Splenic cysts may mimic splenomegaly.
  - 2 types of splenic cysts have been identified.
    - — Congenital (epidermoid)
    - — Acquired (pseudocyst) from trauma or infarction
  - Cysts are generally asymptomatic, and their presence is usually confirmed by radiologic studies.
- Hemangiomas and lymphangiomas.
- Subcapsular hemorrhage.
  - Abdominal trauma may cause subcapsular hemorrhage of the spleen.
  - Accompanied by abdominal pain.
- Accessory spleen may also mimic splenomegaly.
  - Found in 10%–15% of individuals

LABORATORY EVALUATION

- The initial laboratory testing of a child with splenomegaly should include
  - Complete blood cell count
  - Leukocyte differential
  - Reticulocyte count
  - Examination of the peripheral blood smear
- Further laboratory investigations should be directed at the suspected diagnosis, based on findings from
  - History
  - Physical examination
  - Initial laboratory tests

IMAGING

- Imaging of the spleen can be an important adjunct to the physical examination in defining pathologic changes in this organ.
- Radiologic confirmation of a mass in the left upper quadrant should be performed if any question exists about the nature of the mass.
  - Retroperitoneal tumors may be mistaken for an enlarged spleen (eg, neuroblastoma, Wilms tumor).
- Ultrasonography, high-frequency ultrasonography.
  - Used to quantify splenic enlargement.
  - Differentiates the spleen from other left upper-quadrant abdominal masses
  - Contrast-enhanced sonography is a novel technique that allows real-time assessment.
- Radioactive (technetium 99m) sulfur colloid scintigraphy.
  - Used to assess splenic function
- Computed tomography.
  - Used to evaluate splenic trauma and focal splenic pathology.
  - Contrast enhancement detects bleeding sites and hematoma in splenic trauma.
- Magnetic resonance imaging.
  - Can further clarify abnormalities in size and shape
  - Can define parenchymal disease

TREATMENT APPROACH

- Treatment of splenomegaly should be aimed at the underlying disease entity.
  - Patients who have bacterial infections should receive appropriate antimicrobial therapy.
  - Viral causes of splenomegaly generally respond to supportive care.

SPECIFIC TREATMENT

Infectious Mononucleosis

- Patients should refrain from contact or collision sports until illness has completely resolved clinically and the spleen has returned to a normal size.
  - Generally, this is at least 4 weeks from the onset of illness.
  - Sonographic evaluation of spleen size may be necessary to determine when the patient can resume full athletic activity.

Splenectomy

- May be indicated to help control or stage some diseases that cause splenomegaly.
  - Hereditary spherocytosis
  - Autoimmune thrombocytopenia or hemolysis
  - Lymphoma, Hodgkin disease
- Splenectomy may also be indicated to treat chronic, severe hypersplenism.
- Laparoscopic splenectomy is being performed more commonly in children.
  - The procedure is safe and hospital stay is shorter compared with open splenectomy.
- Partial splenectomy has become a viable therapeutic alternative to total splenectomy.
  - Removing ≤90% of an enlarged spleen provides relief from splenomegaly with retention of immune competence.
  - Has been performed with
    - Hereditary spherocytosis
    - Nonparasitic splenic cysts
    - Sickle cell disease
    - Thalassemia

WHEN TO REFER

- Splenomegaly with concomitant adenopathy or hepatomegaly
- Palpation of a hard spleen
- Suspicion of cancer or other infiltrative disorders
- Evidence of hemolytic anemias

WHEN TO ADMIT

- Admission may be required when there is
  - Splenic sequestration in sickle cell disease
  - Injury to the spleen from abdominal trauma
  - Possible cancer

FOLLOW-UP

- All children without spleens
  - Are at risk for fulminant bacteremia (overwhelming postsplenectomy infection), particularly from
    - *Streptococcus pneumoniae*
    - *Haemophilus influenzae* type b
    - *Neisseria meningitidis*
  - Should receive appropriate immunizations.
  - Twice-daily penicillin prophylaxis against pneumococcal infections (in addition to immunization) is recommended 2 weeks before splenectomy.
    - In children <5 years *and*
    - For ≥1 year after splenectomy
    - Possibly throughout childhood and into adulthood for high-risk patients with asplenia

COMPLICATIONS

- Rupture of the enlarged and friable spleen is possible if the child participates in contact sports.
- Hypersplenism can cause cytopenias and severe anemia.

PROGNOSIS

- Prognosis depends on underlying cause.
  - Splenomegaly caused by Epstein-Barr virus or cytomegalovirus infection usually resolves by 4 weeks.

DEFINITION

- Sports medicine is a discipline in itself; an introduction to some common problems is presented here.
- *Concussion* is a clinical syndrome caused by impact to the head.
  - Disturbance of brain function, typically affecting memory and orientation
  - May involve loss of consciousness
- *Post-concussive syndrome* (PCS) is persistence of a cluster of cognitive, physical, sleep, and emotional problems beyond the usual period of recovery following concussion.

SIGNS AND SYMPTOMS

Drug Use in Athletes

- Anabolic steroid use
  - Clues to excessive use include
    - — Jaundice
    - — Increased acne
    - — Behavioral changes (eg, aggressiveness, irritability, marked mood swings)
    - — Gynecomastia
    - — Testicular atrophy
    - — Hirsutism and deepening of the voice (in women)
    - — Liver enzyme elevation
    - — Adverse effects to lipid profile
- Anabolic steroid withdrawal
  - Mood changes
  - Irritability
  - Hot flashes
  - Nausea
  - Myalgia
  - Malaise
  - Tachycardia
  - Hypertension
- Creatine supplements
  - May contain small doses of stimulants that can result in positive test results for banned substances.
  - American College of Sports Medicine recommends against use in athletes <18 years.

Injuries to Bone and Soft Tissue

- Stress fracture
  - Pain during or soon after activity progressing to pain at rest
- Metaphyseal and diaphyseal stress injuries
  - Gradual onset of symptoms.
  - Eventually, pain may preclude running.
- Osgood-Schlatter disease
  - Pain is well localized to the tibial tubercle and typically increases with activity.
  - Significant pain, tenderness, and swelling of the tubercle on the presenting side and, usually, some degree of findings on the contralateral side.
  - Many patients have a history of heel pain compatible with Sever disease (calcaneal apophysitis).
  - No signs or symptoms of intra-articular problems of the knee joint itself.
- Larsen-Johansson disease
  - Well-localized pain at the inferior pole of the patella
  - No signs or symptoms of internal derangement of the knee joint itself
  - On physical examination, point tenderness at the inferior edge of the patella and typically no other abnormal findings
- Calcaneal apophysitis
  - Complaints of heel, ankle, or foot pain.
  - On physical examination, discomfort is typically well localized at the region of the calcaneal apophysis.
  - Pain is typically medial or posterior, although occasionally may be on the lateral side.
  - Tenderness rarely occurs distal near the origin of the plantar fascia.
  - No swelling, warmth, or limitation of motion.
  - Occasionally, because of concurrent tendonitis, some tenderness can occur along the course of the Achilles tendon itself.
  - Pain is reproducible with medial and lateral compression of the heel ("the squeeze test").
- Little League elbow
  - Medial elbow pain
  - Localized tenderness of medial epicondyle
- Little League shoulder
  - Pain in the shoulder related to overhead throwing
- Physeal widening of the distal radius
  - Progressive pain in the wrists.
  - Most often, pain is bilateral, but may be more prominent on one side.
  - On physical examination, point tenderness is often present, and a prominence may be noted on the dorsum of the distal radial physis.
- Osteochondritis dissecans of the capitellum
  - Aching pain in the lateral side of the elbow.
  - With time, patients can lose range of motion.

- Osteochondral fragments can displace acutely, resulting in a loose body sensation, a locked elbow, significant synovitis and pain, or any combination.

- Achilles tendonitis
  - Symptoms are typically located 2–6 cm above the insertion of the Achilles tendon into the calcaneus.
  - Lack of flexibility in the gastrocnemius muscle group may be found on physical examination.
- Rotator cuff tendonitis
  - Pain with overhead activities.
  - In many instances, the athlete will report the arm becoming heavy or tired or feeling dead.
  - Full thickness tears are almost never seen in patients <18 years.
  - Positive impingement test result: pain when bringing the shoulder fully overhead.
    - Examination should include
      - A thorough examination of the neck and shoulder
      - Range-of-motion limitation, muscle atrophy, and focal tenderness in the subacromion region, anteriorly and laterally
      - Tenderness along the biceps tendon
      - Supraspinatus strength
      - Glenohumeral laxity

Acute Trauma

- Ankle sprains
  - Persistent anterolateral ankle pain can occur after even mild ankle sprains.
  - Stress tests (eg, anterior drawer, talar tilt) confirm diagnosis and grade severity.
    - Anterior drawer
    - Brisk motion to pull the heel forward with ankle relaxed in 10° plantar flexion and distal lower leg stabilized with nondominant hand
    - Positive result if more anterior displacement is noted compared with uninjured side
  - Talar tilt assesses calcaneal fibular ligament.
    - Brisk motion to invert calcaneus and talus on the fibula with ankle in neutral or slight dorsiflexion and distal lower leg stabilized with nondominant hand
    - Positive result if more inversion compared with uninjured ankle
- Anterior cruciate ligament (ACL) injuries
  - Patients report an acute "pop" and moderate to severe pain after rotational injury on a fixed foot, often causing them to fall to the ground.
  - Knee typically swells within the first few hours because of the development of hemarthrosis with significant limitation in range of movement.
  - Tenderness is sometimes not marked, and athletes will attempt to return to competition only to discover that the knee is not stable.
    - This may worsen the injury.
  - Lachman test.
    - Performing this test competently requires experience.
      - Patient lies supine and the knee is gently flexed to ~30°.
      - The patient must relax quadriceps and hamstrings enough to allow the examiner to attempt to slide the proximal tibia anteriorly.
      - Although the amount of tibial movement is important, the key factor is the end point.
        - If the test result is negative (ie, ligament is intact), a distinct end point or cessation of forward movement should be felt.
        - The end point should feel similar to holding 2 ends of a short piece of rope and quickly pulling the ends apart until movement suddenly stops.
      - Test result may be falsely negative soon after injury when the knee is painful and swollen.
      - Success depends on
        - Size of patient's leg
        - Ability of patient to relax
        - Size of examiner's hands
      - If doubt exists, knee should be reevaluated later or the patient referred to an orthopedist.
- Meniscal tears
  - Usually occur when knee is twisted during weight bearing.
  - Patient reports popping sensation, feeling of knee giving out, and "locking" with inability to fully extend the knee.
  - McMurray test
    - With patient supine, flex knee and apply valgus stress on lateral aspect of the knee.
    - Knee is flexed and extended while alternately internally and externally rotating the tibia.
    - A "click" indicates positive result.

- Apley test
  - With patient prone and knee flexed 90°, pressure is applied to the heel while the tibia is rotated.
  - Presence of pain with this maneuver is positive result.

- Quadriceps contusion
  - Limitation of knee flexion is used to separate minor from major hematomas.
    - Test 12–24 hours after injury.
    - Mild: >90°.
    - Moderate: 45°–90°.
    - Severe: <45°.
- Avulsion fracture of the pelvis
  - Acute onset of pain following a sudden athletic movement, such as
    - An explosive start for a sprint
    - An extreme pike maneuver (hips flexed and knees extended) in gymnastics
    - A combination twisting movement and direct blow to the iliac crest
  - Focal tenderness to palpation over the affected apophysis
  - Pain with resisted strength testing of the corresponding muscle insertion or origin
- Muscle strain
  - Hamstring strain causes pain at the junction of the middle and distal thirds of the posterior thigh.
- Patellar dislocation
  - The patellae typically dislocates to the lateral side.
  - Patellar apprehension test result is almost always positive.
    - Patient expresses fear that the patella may dislocate as examiner applies gentle lateral pressure.
- Shoulder dislocation
  - 90% are anterior; posterior dislocations tend to occur with seizures or trauma.
  - Patient holds affected arm in a cradle position.
  - Loss of shoulder contour.
- Patellofemoral pain syndrome
  - Typical onset is insidious and without a specific history of trauma.
  - No history of erythema, warmth, induration, or true effusion.
  - Slightly puffy knee in some patients.
  - No mechanical complaints of catching or locking.
  - Popping may be present and is usually painful.
  - On physical examination
    - Tenderness along the medial and lateral sides of the patellofemoral articulation.
    - Mild discomfort over the anterior portion of the joint line, but typically no tenderness over the middle or posterior portion of the tibial femoral articulation.
    - The joint has full range of motion with no crepitation.
    - Stable knee.

Concussion

- Physical symptoms
  - Headache
  - Nausea
  - Vomiting
  - Ataxia
  - Visual problems
  - Photophobia and phonophobia
  - Numbness/tingling
  - Dazed, stunned
- Cognitive symptoms
  - Feeling slowed down, mentally "foggy"
  - Difficulty concentrating
  - Memory disturbances
  - Confusion about recent events
  - Slow response to questions
- Emotional symptoms
  - Irritability
  - Sadness
  - Nervousness
- Sleep changes
  - Drowsiness
  - Sleeping more or less than usual
  - Trouble falling asleep

DIFFERENTIAL DIAGNOSIS

Injuries to Bone and Soft Tissue

- Osgood-Schlatter disease
  - Tumor or infection can mimic Osgood-Schlatter disease.
- Larsen-Johansson disease
  - Irregular ossification at the inferior pole of the patella may be mistaken for a fracture.
- Calcaneal apophysitis
  - Significant irregularity of the ossifying calcaneal apophysis is a normal finding in children and should not be confused with evidence of a fracture.
  - Need to rule out other osseous processes, such as tumor or infection.

- Little League shoulder
  - Internal impingement conditions present similarly.
    - Rotator cuff tears
    - Labral tears
    - Biceps tendonitis
    - Anterior instability
    - Scapular dysfunction
  - Impending pathologic fracture from a simple bone cyst in the upper humerus.
- Physeal widening of the distal radius should be distinguished from
  - Carpal laxity with dorsal wrist capsular impingement
  - Posterior interosseous neuroma
  - Avascular necrosis of the lunate
- Tendonitis
  - Need to rule out other bony abnormalities

Acute Trauma

- Collateral ligament injuries of the knee
  - Consider concurrent injury to the cruciate ligaments, menisci, and articular surfaces.
  - Lateral knee and ligament injuries are uncommon in young athletes; they should raise suspicion of another explanation for the patient's signs and symptoms, and referral is wise.
- ACL injuries
  - A high index of suspicion should be maintained for ACL injury, and it must be ruled out before a young athlete who has a knee injury returns to practice or competition.
- Quadriceps contusion
  - Differentiating a large quadriceps hematoma from a malignant tumor (eg, Ewing sarcoma and osteosarcoma) becomes challenging, as those tumors have a propensity to occur in teenagers and may bleed internally.
- Muscle strain
  - Muscle strains are not as common in young athletes as they are in older ones.
  - An unknown musculoskeletal malady is often misdiagnosed as strain.
  - Particularly around the hip and thigh area, the examiner should be careful not to miss a slipped capital femoral epiphysis, an avulsion fracture, an infection, or a tumor as causes of pain.
  - More proximal hamstring tenderness should raise suspicion of an occult injury to the ischial apophysis.
- Patellar dislocation
  - Should not be labeled as knee dislocation, which denotes displacement of the articulation between the tibia and femur.
    - The latter is a high-energy injury and has high associated morbidity, including, occasionally, loss of limb.

Anterior Knee Pain

- Can arise from many disorders, including
  - Osgood-Schlatter disease
  - Larsen-Johansson disease
  - Patellar tendonitis
  - Patellar instability
  - Chondromalacia patella
  - Patellofemoral pain syndrome
- Less common disorders
  - Quadriceps tendonitis
  - Bipartite patella
  - Osteochondritis dissecans of the femur or patella
  - Iliotibial band tendonitis
  - Prepatellar bursitis
  - Popliteus tendonitis
  - Osteomyelitis
  - Septic arthritis
  - Inflammatory arthritis
  - Tumors

IMAGING

Injuries to Bone and Soft Tissue

- Metaphyseal and diaphyseal stress injuries
  - Magnetic resonance imaging (MRI) may be the most sensitive study for stress fractures.
  - Bone scan may detect early stress fracture of the metaphysis or diaphysis.
    - Bone scan findings must be correlated to clinical symptoms.
    - ≤50% of adolescents with stress fractures will show multiple areas of stress response on bone scan, many of which do not correlate to areas of symptoms.
- Osgood-Schlatter disease
  - Lateral radiograph of the knee can show irregularity of the tibial tubercle.
- Larsen-Johansson disease
  - Lateral radiograph of the knee may show irregular ossification at the inferior pole of the patella.
- Calcaneal apophysitis
  - No classic radiographic change of calcaneal apophysitis.

- In bilateral cases, radiographs are necessary only if some atypical component of the history and physical raises concern about another diagnosis.

- Physeal widening of the distal radius
  - Anteroposterior and lateral radiographs show physeal widening.
  - Comparison radiographs of the other side are almost always obtained, although both sides may be involved.
  - Typically, some asymmetry is noted.
- Osteochondritis dissecans of the capitellum
  - Plain-film radiographs often show a lesion of the capitellum.
    - Sclerotic region or simple radiolucency may be present.
    - Tangential views may be necessary to see the lesion.
  - Computed tomography (CT) or MRI is sometimes helpful.
- Tendonitis
  - Radiography and MRI are rarely indicated.
- Internal impingement
  - Plain-film radiographs are not diagnostic but may rule out other bony abnormalities.
  - MRI is diagnostic but often not necessary.

Acute Trauma

- Ankle sprains
  - All skeletally immature athletes need radiography to rule out fibular fracture.
- Collateral ligament injuries of the knee
  - Plain-film radiographs may not be diagnostic.
  - Stress radiography or MRI is usually needed to make this diagnosis.
- ACL injury
  - Radiography in skeletally immature athletes to rule out tibial eminence fracture
    - May reveal a Segond fracture (avulsion of the lateral aspect of proximal tibia), pathognomonic of intra-articular injury
- Meniscal tears
  - If a meniscal tear is suspected, referral or MRI is appropriate.
  - Some studies suggest MRI may be less sensitive and specific in children than adults, so judicious use is recommended.
  - Arthrograms are obtained much less commonly than before.
- Avulsion fracture of the pelvis
  - Diagnosis can often be confirmed with plain-film radiographs.
  - Special oblique views and, occasionally, CT or MRI are helpful.
- Patellar dislocation
  - Unless patellar dislocation or subluxation is trivial with little joint pain, radiographs should be obtained to assess for osteochondral fragments.
- Shoulder dislocation
  - Unless the episode is minor, radiographs confirm reduction and rule out associated fracture.
- Anterior knee pain
  - Diagnostic imaging, including MRI, often does not reveal source.
  - These studies are sometimes indicated to rule out other definable abnormalities.
- Patellofemoral pain syndrome
  - Plain-film radiographs are usually negative; further diagnostic evaluation is not indicated.

CLASSIFICATION

- Severity grading of sprains
  - Grade I (mild)
    - Stretching of the ligament with minimal microscopic injury
    - Clinical presentation: mild swelling, limp
    - Typical recuperation time: 0–2 weeks
  - Grade II (minor)
    - Partial disruption of the ligament
    - Clinical presentation: modest swelling, diffuse tenderness, difficulty in weight bearing
    - Typical recuperation time: 1–4 weeks
  - Grade III (severe)
    - Complete disruption of the ligament
    - Clinical presentation: extensive swelling and bleeding, instability, and disability
    - Typical recuperation time: 4–12 weeks

SPECIFIC TREATMENTS

Injuries to Bone and Soft Tissue

- Overuse syndromes
  - Stress fracture
    - Avoidance of painful activities until healing occurs
    - Return to sport after being pain-free for a month
  - Metaphyseal and diaphyseal stress injuries
    - Managed by rest
    - Crutches often necessary
    - Casts and immobilization sometimes needed

- Surgical intervention required occasionally
  - Suspected stress fracture of proximal femur is probably best managed by an orthopedic surgeon.
  - Screw stabilization may be needed for slipped epiphysis or stress fracture.
  - Stress fractures of fifth metatarsal tend to be recurrent and often best managed with an intramedullary screw.

- Osgood-Schlatter disease
  - Symptoms are often relieved with
    - Application of an ice pack
    - Intermittent use of oral nonsteroidal anti-inflammatory drugs (NSAIDs)
    - Application of compression band
    - Activity modifications as indicated by symptoms
    - Hamstring stretching
  - Casts are not routinely used because immobilization may weaken ligament insertions.
  - Brief periods of rigid immobilization may be necessary for acute exacerbations.
- Larsen-Johansson disease
  - Treatment with ice, NSAIDs, and activity modification.
  - Immobilization and surgery are rarely necessary.
- Calcaneal apophysitis
  - Ice, NSAIDs, and activity modification are dictated by symptoms.
  - Shoe inserts that provide padding beneath the heel can be helpful; a 3/8" silicone or felt pad works best.
  - Casts or ankle motion walkers (a removable rigid walking splint) are occasionally necessary for severe cases.
  - Surgery is not indicated.
- Little League elbow
  - Refrain from throwing until symptoms resolve.
  - Muscle strengthening and pitch training.
  - Adherence to league regulations limiting number of pitches thrown.
- Little League shoulder
  - Managed by rest of the shoulder
- Physeal widening of the distal radius
  - Treatment goal is resolution of symptoms and normalization of radiographs.
- Osteochondritis dissecans of the capitellum
  - May heal with prolonged rest.
  - Surgery is indicated for continued locked elbow, symptomatic loose bodies, and persistent pain and limitation of movement.
- Tendonitis
  - In young athletes, treatment is entirely nonoperative.
  - If analysis of lower-extremity mechanics during gait suggests hyperpronation, custom foot orthoses can help.

Acute Trauma

- The fundamental principles of treatment for many musculoskeletal injuries go by the acronym RICE (**r**est, **i**ce, **c**ompression, and **e**levation).
  - Rest
    - Especially important for the first 24–72 hours after significant injury.
    - For lower-extremity injuries, crutches should be used to avoid weight bearing.
  - Ice
    - May be applied for 20 minutes every 2–4 waking hours.
    - Use a wet cloth between ice and skin to decrease chance of cold injury.
    - Continue using ice until swelling disappears completely.
  - Compression
    - Applied with an elastic bandage
  - Elevation
    - Place the injured extremity above the level of the heart to aid in reducing edema.
- Ankle sprains
  - Treatment options are complicated and chosen on the basis of
    - Severity of injury (See the Classification section.)
    - Demands of the athlete
    - Experience of the health care team
  - Minor sprains
    - Apply RICE principles and periodically reevaluate.
    - At reevaluation, if pain is minimal, test the ankle for stability.
    - Observe athlete in functional tasks (eg, running, cutting, twisting).
    - If tasks are performed well without significant pain, the individual may return to competition.
  - Moderate sprains
    - For the less serious athlete, use an expectant approach.
      - Crutches
      - Elastic bandage wrap
      - Gradual progression of weight bearing
      - Cast or controlled ankle motion walker
      - Return to sports only after symptoms resolve

  - For the serious athlete, referral to a physical therapist is often helpful.
- Severe sprains
  - Should be managed by someone with advanced skills in dealing with musculoskeletal problems.
  - A period of immobilization to reduce bleeding and swelling is often helpful.
  - Assessment for chronic laxity and tarsal coalitions should be made.
- Persistent anterolateral ankle pain can occur after even mild ankle sprains.
  - If symptoms persist, refer to orthopedist or sports medicine specialist.

- Collateral ligament injuries of the knee
  - First, use RICE principles.
  - Depending on severity of injury, mobilize knee as swelling and tenderness diminish.
  - Assess strength as range of motion returns.
  - For moderate and severe sprains, consider using a dual, upright, hinged, functional knee orthosis.
- ACL injuries
  - RICE and weight bearing as tolerated.
  - Joint aspiration may relieve pain in athletes with a large hemarthrosis.
  - Comprehensive rehabilitation should be started early and include weight bearing and range-of-motion exercises.
  - Exercises that encourage balance, coordination, and reaction sharpen responses in surrounding structures.
  - For very young patients, bracing, physical therapy, and activity modification is probably the best approach.
- Meniscal tears
  - Pattern and location of injury determine whether meniscus will heal on its own or require arthroscopic removal or repair.
  - Goals are to preserve as much of the normal functioning rim of cartilage as possible while alleviating mechanical snapping and subsequent degeneration.
  - Symptomatic discoid lateral menisci require surgery.
- Quadriceps contusion
  - RICE and crutches for initial treatment of quadriceps hematoma.
  - As pain and swelling diminish, begin active knee flexion exercises.
- Avulsion fracture of the pelvis
  - Crutches and rest for the first few weeks.
  - Stretching may inhibit healing and should be avoided until patient is pain-free.
- Muscle strain
  - For hamstring strain, RICE and crutches
- Patellar dislocation
  - Manipulative reduction can often be achieved.
    - Procedural sedation and gentle extension of the knee result in reduction.
  - Significant patellar dislocation.
    - Immobilize the knee.
    - Use RICE principles.
- Shoulder dislocation
  - Traditional treatment: 3 weeks of immobilization, followed by a rigorous physical therapy program
- Chondromalacia patella
  - In mild cases, pain from chondromalacia patella will abate with
    - Intermittent NSAIDs
    - Quadriceps-strengthening program
    - Judicious activity modification
- Patellofemoral pain syndrome
  - Stretching and strengthening quadriceps muscles often reduce anterior knee pain.
  - Principles are to strengthen the vastus medialis and improve patellar tracking.
  - Taping or supportive knee sleeves sometimes provide relief.
  - Intermittent and judicious use of NSAIDs may help.
  - In some cases, adjustment of expectations and activities is necessary.
  - In refractory cases, referral to a musculoskeletal specialist may become appropriate.

Concussion

- Athletes need help from parents and coaches to monitor recovery.
- Adequate sleep and limited physical and cognitive exertion speed recovery.
- Symptomatic students may require accommodation with schoolwork until cognitive function returns.

WHEN TO ADMIT

- Fractures requiring open reduction
- Fractures associated with neuro injury or vascular injury
- True knee dislocation
- Traumatic brain injury in conjunction with internal organ injuries

WHEN TO REFER

- When the diagnosis of the musculoskeletal injury is uncertain
- When injuries involve the growth plate in which future growth may be compromised
- When the patient is not responding to initial treatment
- When uncertainty exists in the safety of the young athlete to return to a competitive sports environment
- When an ACL tear or meniscal tear is suspected

FOLLOW-UP

Injuries to Bone and Soft Tissue

- Metaphyseal and diaphyseal stress injuries
  - Well-designed plan of alternative training, gradual resumption of participation in sports, and monitoring for recurrent symptoms
- Physeal widening of the distal radius
  - Once the athlete returns to gymnastics, clinical and radiographic monitoring are required.

Acute Trauma

- Ankle sprains
  - Referral to a physical therapist.
  - Range of motion is begun early, and strengthening is emphasized.
  - As the ankle becomes comfortable, the proprioception training phase of rehabilitation begins.
  - Optional taping.
  - In all cases: functional criteria for return to sports, prevention of reinjury, and reassessment of progress.
- Collateral ligament injuries of the knee
  - A physical therapist or athletic trainer can help design an adequate rehabilitation program.
- Quadriceps contusion
  - Monitoring for reinjury
- Avulsion fracture of the pelvis
  - Athlete should be gradually returned to activity and monitored for recurrence of symptoms.
- Muscle strain
  - Once the patient is comfortable, gradual stretching and strengthening program is initiated.
  - Return to activities as tolerated.
  - Monitor for recurrent symptoms.
- Patellar dislocation
  - As pain and swelling subside, rehabilitation that emphasizes strengthening of the quadriceps muscles, particularly the vastus medialis.
  - A patellar-stabilizing knee sleeve is used during the initial phases of return to activity.
- Shoulder dislocation
  - After 3 weeks of immobilization, rigorous physical therapy program begins.
    - Principle: Strengthen rotator cuff muscles to help compensate for laxity of the shoulder joint capsule (ligaments).
    - Recurrent instability despite a therapy program is generally an indication for surgical stabilization.
- Chondromalacia patella
  - Completely eliminating symptoms may not be possible.
  - Although a therapy program can be helpful, the patient must have a clear understanding that the goal is to reduce symptoms.
  - Surgical intervention to alter the patella's articular surface is sometimes indicated.

Concussion

- Athletes who exhibit worsening of symptoms (eg, headache, vomiting, altered mental status, irritability, focal neurologic signs)
  - Refer to emergency department for evaluation.

COMPLICATIONS

- PCS
  - Presence of ≥3 symptoms 3 months after injury.
    - Headache
    - Dizziness
    - Fatigue
    - Irritability
    - Difficulty concentrating and performing mental tasks
    - Impairment of memory
    - Insomnia
    - Reduced tolerance to stress, emotional excitement, or alcohol
  - Risk factors include adolescent age, loss of consciousness, posttraumatic amnesia, initial symptom of headache, high levels of initial symptoms, and history of prior concussion.
  - Efficacy of symptomatic pharmacologic and rehabilitative interventions is unknown.
  - Exercise may be beneficial, provided the athlete avoids impact during period of vulnerability for repeat injury.

PROGNOSIS

Injuries to Bone and Soft Tissue

- Metaphyseal and diaphyseal stress injuries
  - Healing time ranges from 4–12 weeks.
- Osgood-Schlatter disease
  - In most patients, will run its course with time.
  - Symptoms can last 1–4 years.
  - In ~3% of patients, a persistent ossicle will form that can remain symptomatic and may ultimately require surgical excision.
  - Fracture of the tibial tubercle has been reported.
    - Incidence is not known, but it appears to be low.
  - Remaining active in sports is possible.
- Larsen-Johansson disease
  - Self-limited and typically lasts 3–12 months.
  - In general, athletes may participate in sports as tolerated.
- Calcaneal apophysitis
  - Almost always resolves with time.
  - Complications are extremely rare.
- Little League shoulder
  - If symptoms are minimal, the patient can often be allowed to bat and play in an infield position that involves minimal throwing.
  - Clinical and radiographic resolution can take ≤6 months.
  - Carefully planned resumption of pitching can then begin with monitoring for recurrence of symptoms.
- Physeal widening of the distal radius
  - Goal of treatment is resolution of symptoms and normalization of radiographs, which usually takes ≥3 months.
- Osteochondritis dissecans of the capitellum
  - Can result in permanent arthrosis of the elbow joint

Acute Trauma

- Ankle sprains
  - Risk of reinjury is 5× higher.
  - 20%–40% of athletes experience chronic ankle instability after injury.
  - Return to sports for lateral ankle sprains averages
    - 8 days for grade I
    - 15 days for grade II
    - 28 days for grade III
- Collateral ligament injuries of the knee
  - Most heal satisfactorily.
- ACL injuries
  - Left without ACL stability, most knees in young, active patients eventually become symptomatically unstable, and reinjury will occur.
  - Most ACL injuries do not heal well, and primary surgical repairs (as opposed to reconstructive surgery) are not effective.
  - In older and less active individuals, nonoperative management plays a role; however, most ACL injuries in young athletes should be reconstructed.
  - Return to sports.
    - 6–12 weeks for those treated nonoperatively
    - 6–8 months following surgical reconstruction
- Meniscal tears
  - Young patients have the potential to heal.
  - Pattern and location of tear determine whether meniscus may heal on its own or will require arthroscopic partial removal or repair.
- Quadriceps contusion
  - Full return of motion is the minimal requirement for return to contact sports with use of a padded guard.
  - Return to sports averages
    - 13 days for mild
    - 19 days for moderate
    - 21 days for severe
- Avulsion fracture of the pelvis
  - Most do not displace significantly; almost all heal with time and rest.
- Muscle strain
  - Mild injuries heal fairly rapidly, whereas severe strains can lead to large areas of scar tissue that are prone to reinjury.
  - Reduction of tenderness can take days to weeks, depending on initial severity.
  - Reinjury is likely in 12%–31% of hamstring strains.
    - Return to play
      - 2–3 days for mild
      - 3–12 weeks for severe
- Patellar dislocation
  - 90% resolve spontaneously.
  - Recurrent patellar instability, particularly in those with a familial history, may require reconstruction.

Concussion

- Symptoms generally last 72 hours and most resolve ≤7–10 days.
  - Recovery may be prolonged in some who have persistent concussive symptoms.

PREVENTION

- 4 basic principles of injury prevention measures.
  - Passive strategies are more effective than those requiring repeated actions.
  - Specific advice is more effective than generalized information.
  - Injury control must also include post-injury care and rehabilitation.
  - Attention should focus on common problems for which effective interventions are available.
- Although many sports injuries are random events, nearly two-thirds of all injuries might be reduced by improvements in
  - Conditioning
  - Equipment
  - Compliance with rules
  - Coaching and supervision
  - Rehabilitation of existing injuries
  - Efforts to prevent reinjury
- Many schools now use certified athletic trainers for prevention of and rehabilitation from sports injuries.
- Injuries to bone and soft tissue.
  - Overuse syndromes
    - Prevention involves education of young athletes, parents, coaches, and the entire health care team.
    - Understanding these principles is crucial to returning to sports successfully after experiencing overuse conditions.
    - Failure to change underlying problems leads to reinjury.
  - Osteochondritis dissecans of the capitellum
    - Junior baseball programs typically have rules limiting duration of pitching.
      - Usual limit is 3 innings per game and ≤6 innings per week.
    - Young athletes, parents, and coaches need to be educated about this condition to avoid excessive pitching.
- Concussion
  - Protective head gear
  - Preparticipation evaluation to facilitate prompt recognition and reporting of concussive injury
  - Standardized Assessment of Concussion performed at the sidelines following injury

Stomatitis

DEFINITION

- Inflammation of the oral mucosa, characterized by multiple ulcerations inside the mouth
  - Frequently painful
  - May lead to decreased oral intake and dehydration

SIGNS AND SYMPTOMS

- Recurrent aphthous stomatitis (RAS)
  - Oral lesions are the only physical examination finding.
    - Assess for ≥1 painful ulcers on the buccal, labial, and lingual surfaces, as well as on the floor of the mouth.
  - 3 clinically distinct types of RAS.
    - Minor variety
      - Small, round craters, <5 mm in diameter and surrounded by an erythematous halo.
      - Heal in 1–2 weeks.
    - Major variety
      - Lesions >5 mm that often scar
      - May last 6 weeks
    - Herpetiform variety
      - Herpes-like appearance of multiple, small clusters of pinpoint lesions.
      - Resolve in 7–10 days.
      - Not caused by the herpesvirus.
  - Children with RAS are otherwise healthy.
- Herpes simplex virus type 1.
  - Fever, malaise, sore throat, and cervical adenopathy are present.
  - Vesicles can develop anywhere on the oral mucosa, most typically in the anterior oropharynx on the lips, tongue, and buccal mucosa.
  - Gingiva may be swollen and erythematous.
  - The perioral area may also display vesicles and small ulcers that coalesce and continue to appear for the next week.
  - Oral pain is present.
    - May result in anorexia and dehydration
  - Spontaneous resolution in 7–10 days.
- Coxsackievirus.
  - Herpangina.
  - Ulcers surrounded by erythematous halos located in the posterior oropharynx.
  - Spontaneous resolution in 3–5 days.
  - Hand-foot-and-mouth disease.
    - Along with lesions of the posterior oropharynx, blanching red macules or vesicles appear on the palms, soles, and buttocks.
    - Erythematous halos may surround the macules.
    - Resolve spontaneously within a week.
  - Fever, malaise, dysphagia, and anorexia accompany coxsackievirus infections and can lead to dehydration in children.
- Necrotizing ulcerative gingivitis.
  - Painful, erythematous, and friable gingiva.
  - Necrotic tissue accumulates as a pseudomembrane over the gingival surface.
  - Foul breath.
  - Fever, malaise, anorexia, and dehydration may be present.
- Candidal mucositis.
  - White, curd-like patches on many of the surfaces of the oral mucosa.
    - If white patch is scraped and removed, an ulceration will be present at the base.
  - Diaper dermatitis may also be present.
- Contact stomatitis
  - Can present in 4 general ways.
    - Red lesions with general mouth erythema
    - White lesions and leukoplakia
    - Erosions and ulcerations
    - No obvious lesions accompanied by mouth pain and burning
  - The manifestation of stomatitis in the multitude of potential underlying multisystem diseases will vary depending on the diagnosis.
  - Immunocompromised patients may
    - Experience more frequent and severe episodes of oral ulceration.
    - Take longer for episodes to resolve.
- Appearance of individual aphthae in stomatitis secondary to a benign or self-limiting condition may be indistinguishable from that associated with a serious underlying systemic disease.
  - Important to identify other symptoms and use physical examination findings to determine the appropriate etiology
- Periodic fever accompanied by aphthous stomatitis, pharyngitis, and (cervical) adenopathy (PFAPA) syndrome.
  - Recurrent fevers every 4–6 weeks with onset in the first 6 years of life.
  - May cause general malaise, anorexia, headache, abdominal pain, and arthralgias.
  - Symptoms typically resolve within 1 week.
  - The child has complete resolution of symptoms between recurrences.

DIFFERENTIAL DIAGNOSIS

- RAS infection
  - Viruses
    - Herpes simplex type 1
    - Varicella zoster, coxsackievirus
    - Other enteroviruses
    - Rubeola
    - Epstein-Barr
    - HIV
  - Bacteria
    - *Borrelia vincentii*
    - *Fusobacterium dentium*
    - Syphilis
    - Gonorrhea
    - Tuberculosis
  - Fungi
    - *Candida*
    - Histoplasmosis
- Irritant contact stomatitis
- Allergic contact stomatitis
- Iatrogenically induced stomatitis
- Systemic disorders
  - Behçet syndrome
  - Inflammatory bowel disease
  - Celiac disease
  - Diabetes mellitus
  - Systemic lupus erythematosus
  - Scleroderma
  - Dermatomyositis
  - Granulomatosis with polyangiitis (Wegener)
  - PFAPA syndrome
  - Cyclic neutropenia
  - Nutritional deficiencies
  - Dermatologic disorders

LABORATORY FINDINGS

- In most cases, laboratory evaluation is not helpful in diagnosis or management.
- Measure serum electrolytes in patients with severe dehydration during the rehydration process.
- If frequently recurring or persistent oral aphthae are present, along with genital lesions or other systemic findings, an evaluation for the underlying cause may include
  - Complete blood cell count
  - Erythrocyte sedimentation rate
  - Serum levels of
    - Iron
    - Folate
    - Vitamin B_{12}
    - Zinc
  - Depending on the history, screening for the following criteria may be necessary:
    - Antinuclear antibodies
    - HIV
    - Celiac disease

TREATMENT APPROACH

- Goals of treatment include
  - Relieving pain
  - Preventing dehydration
- By maximizing pain relief, the child will be able to remain hydrated and consume a soft diet.

SPECIFIC TREATMENTS

Pain Relief

- Systemic ibuprofen, acetaminophen, or opiates
- Application of topical substances
  - Swish and then spit *or*
  - Paint the substance on the sores with a cotton-tipped swab.
  - Topical agents that have been studied minimally for safety and efficacy include
    - Saline rinses
    - Diphenhydramine–aluminum hydroxide with magnesium hydroxide–viscous lidocaine compounded in various combinations
    - Benzocaine
    - Kaolin
    - Pectin
  - Most of these agents, if used too aggressively, can lead to overdose and adverse side effects.
  - Topical anesthetic preparations, in particular, must be used cautiously.
    - Risk of aspiration, loss of protective airway reflexes, and systemic toxicity (eg, methemoglobinemia) caused by absorption through inflamed oral mucosa
- In the immunocompromised child or child with stomatitis secondary to cancer treatment
  - Use topical and systemic analgesics for pain relief.
    - Topical sucralfate and capsaicin have been found to relieve pain of chemotherapy- or radiation-induced mucositis.
    - These agents are not routinely used for children with benign, self-limited conditions.
  - Monitor for secondary infection.

Antimicrobial Treatment

- Antimicrobials are of limited value.
  - In patients with necrotizing ulcerative gingivitis, the following treatments may be required:
    - — Chlorhexidine mouth rinses
    - — Systemic antibiotics, such as penicillin
- Oral acyclovir is of limited therapeutic benefit in the otherwise healthy child with herpes stomatitis.
  - Topical acyclovir is ineffective.

PFAPA Syndrome

- Typically responds well to a short course of oral steroids (1–2 mg/kg/d for 5 days) if prescribed at the onset of symptoms

WHEN TO ADMIT

- Hospitalization may be required for intravenous rehydration therapy in a child who cannot eat and drink because of severe pain from mouth lesions.

WHEN TO REFER

- Referral to an oral surgeon or otolaryngologist should be considered when
  - Underlying cause of the stomatitis is uncertain *or*
  - If oral lesions persist for >2 weeks.
  - Biopsy of the lesion may be necessary.
    - — Especially for a child who uses smokeless tobacco
- Children with stomatitis plus multiple symptoms and abnormal physical examination findings may require specialty expertise to establish the definitive diagnosis and administer appropriate treatment.
  - Allergist-immunologist
  - Rheumatologist
  - Dermatologist
  - Gastroenterologist
  - Ophthalmologist

PREVENTION

- Most causes of stomatitis cannot be prevented.
- In general, promote
  - Avoidance of tobacco products and any possible irritants
  - Good oral hygiene to reduce the risk of dental caries and gingivitis
- Minimize exposure to the proposed triggers for RAS.
- On the basis of studies in adults, continuous oral acyclovir is a therapeutic option for preventing recurrences in a child with frequent herpetic flares.
- Children with cancer may benefit from a preventive protocol that includes
  - Frequent plaque biofilm removal and toothbrushing
  - Chlorhexidine or saline rinses
  - Nystatin

DEFINITION

- Stridor is typically a high-pitched, monophonic noise caused by turbulent airflow through a partially obstructed extrathoracic airway, heard predominately on inspiration.

HISTORY

- Age at initial presentation and a description of the events surrounding onset of symptoms can provide important clues to the underlying diagnosis.
- Laryngomalacia.
  - The most common cause of congenital stridor in infancy.
  - Stridor begins in the first few weeks of life and occurs only during specific states of alertness, such as eating, sleeping, or excitement.
  - Stridor with laryngomalacia is typically intermittent and worsens over the first few months of life.
    - With age, episodes become less severe and less frequent.
    - Stridor usually resolves completely by the first birthday.
- Viral croup.
  - Stridor preceded by fever, upper respiratory symptoms, and a barky or seal-like cough.
  - No stridor between episodes.
  - The patient may have history of similar episodes in the past.
  - Stridor caused by viral croup improves within days.
- Subglottic stenosis or granulation tissue.
  - Stridor that develops shortly after a prolonged intubation
  - May be continuous
  - Often seen in preterm neonates who required mechanical ventilation during the neonatal period
- Foreign body.
  - Sudden onset
  - History of choking or placing small object in mouth
- Retropharyngeal abscess.
  - Fever
  - Difficulty swallowing
- Hemangioma.
  - Stridor is mild at birth and worsens during first 6 months
  - History of cutaneous hemangiomas
- Bilateral vocal cord paralysis.
  - History of injury to recurrent laryngeal nerves
  - Arnold-Chiari malformation or increased intracranial pressure
- Vocal cord cyst.
  - Hoarse voice
  - Chronic irritation to vocal cords or airway instrumentation
- Recurrent respiratory papillomatosis.
  - Usually associated with stridor or hoarseness 2–3 years after birth.
  - Infection is acquired through vertical transmission in the birth canal from maternal cervical human papillomavirus infection.
- Laryngeal web.
  - Develops shortly after birth (congenital)
  - Develops after airway instrumentation (acquired)
- Onset of stridor in an older child or adolescent with no previous history should prompt a more thorough evaluation.

PHYSICAL EXAMINATION

- Assess position.
  - Extension of the neck is often seen with serious infection, such as epiglottitis or retropharyngeal abscess.
  - Improvement with jaw thrust suggests pathology in epiglottis rather than subglottis.
- Look for drooling.
  - Suggests a mass effect or edema in the posterior pharynx, causing dysphagia in addition to stridor
- Keep the patient calm and maintain the airway.
- Examine the oropharynx to detect
  - Retropharyngeal bulge
  - Lateral displacement of the uvula and swelling of a tonsillar pillar from an underlying infection in patients with acute onset
- Externally examine the neck for
  - Presence of suprasternal retractions when obstruction is severe
  - Displacement of the larynx, a mass obstructing the airway, or signs of trauma
- Note the quality of the voice.
  - Hoarseness, aphonia, or a weak cry suggest vocal cord disease.
- Physical examination findings.
  - Laryngomalacia
    - Predominately inspiratory
    - May be positional

- Viral croup
  - — Predominately inspiratory
  - — No change with position
- Subglottic stenosis
  - — Predominately inspiratory but often biphasic
- Foreign body
  - — Predominately inspiratory if obstruction is extrathoracic
- Retropharyngeal abscess
  - — Often presents with stertor
  - — Presence of drooling
- Hemangioma
  - — Cutaneous lesions may be present.

DIFFERENTIAL DIAGNOSIS

- Causes of stridor.
  - Laryngomalacia
  - Viral croup
  - Subglottic stenosis
  - Foreign body
  - Retropharyngeal abscess
  - Hemangioma
  - Bilateral vocal cord paralysis
  - Vocal cord cyst
  - Laryngeal papillomatosis
  - Laryngeal web
  - Laryngeal fracture
- Because the extrathoracic airways extend from the nose to the proximal trachea, high-pitched laryngeal stridor must be differentiated from other abnormal inspiratory noises.
  - Stertor
    - — Noisy, rumbling-type noise similar to snoring
    - — Heard with partial airway obstruction in the oropharynx or nasopharynx
- For stridor that worsens or persists, coexisting or alternate diagnoses should be considered.
  - Mild stridor caused by a subglottic hemangioma may initially be attributed to a more common problem (eg, laryngomalacia).
    - — Similar to laryngomalacia, obstruction from a hemangioma tends to worsen after initial presentation as the lesion enlarges.
    - — Unlike with laryngomalacia, natural resolution of the hemangioma and, thus, the stridor may take several years rather than months.
- History of a hoarse voice or cry suggests glottic disease and might result from chronic irritation of the vocal cords.
- Other clues that suggest more ominous conditions include
  - Constant stridor
  - Failure to thrive
  - Difficulty swallowing
  - Severe and sudden onset of symptoms

LABORATORY EVALUATION

- Laboratory testing has limited value.

IMAGING

- Radiographic findings
  - A simple radiograph of the neck can identify obstructive lesions in the retropharynx, glottis, and subglottic area.
  - Viral croup.
    - — Steeple sign on neck radiograph
  - Subglottic stenosis.
    - — Subglottic narrowing on neck radiograph
  - Foreign body.
    - — May be visualized on radiograph if radiopaque
  - Retropharyngeal abscess.
    - — Retropharyngeal mass on lateral neck radiograph
  - Hemangioma.
    - — Subglottic obstruction on neck radiograph

DIAGNOSTIC PROCEDURES

- Pulmonary function testing
  - Not often necessary but can confirm suspicion of an extrathoracic obstruction
- Flexible laryngoscopy
  - Direct visualization of the airway (including the posterior pharynx and glottis) by flexible laryngoscopy often provides definitive information.
  - Usually well tolerated, and most often with topical anesthesia alone.
  - For laryngomalacia
    - — Laryngoscopy merely confirms presence of laryngomalacia while excluding other causes of airway obstruction.
    - — For severe laryngomalacia, laryngoscopy can also identify specific structural obstruction that might be amenable to surgical correction.
    - — Severe laryngomalacia might obscure the view of the subglottic area such that a more distal lesion would not be visible.
      - Direct visualization of the subglottic region and proximal trachea may be indicated to exclude a second lesion.

- Direct laryngoscopy and bronchoscopy under sedation or general anesthesia can help diagnose and quantify the severity of subglottic stenosis or identify other subglottic lesions that cause obstruction.

- Findings on diagnostic tests
  - Laryngomalacia
    - Obstruction of glottic space by collapsing supraglottic structures on laryngoscopy
  - Subglottic stenosis
    - Flat inspiratory and expiratory loop on spirometry
    - Subglottic narrowing on direct laryngoscopy
  - Hemangioma
    - Seen on direct laryngoscopy
  - Bilateral vocal cord paralysis
    - No movement of vocal cords during laryngoscopy
  - Vocal cord cyst
    - Visible on laryngoscopy
  - Laryngeal papillomatosis
    - Visible on laryngoscopy
  - Laryngeal web
    - Visible on laryngoscopy

TREATMENT APPROACH

- Ensure airway patency before reaching a differential diagnosis.
  - Stridor reflects obstruction of a large centralized airway.
  - Stridor can range in severity from mild to life-threatening.
- For most cases of stridor
  - Obtain a succinct, focused history.
  - Perform physical examination.
  - Perform directed diagnostic tests.
- For the child with signs of severe respiratory compromise—distressed appearance, severe retractions, nasal flaring, pallor or cyanosis, altered mental status—initially focus on
  - Maintaining the airway
  - If possible, relieving the obstruction
  - Intubation
    - Attempted only by personnel skilled at airway management.
    - Performed in as controlled a setting as possible.
    - If potentially difficult, surgical support should be present in case tracheostomy is required.

SPECIFIC TREATMENT

Laryngomalacia

- Most cases can be managed with observation alone, with particular attention to adequate caloric intake and weight gain.

Viral Croup

- Most cases of croup can be managed with close observation alone.
- With more severe obstruction (nasal flaring, retractions)
  - Racemic epinephrine may temporarily relieve symptoms of obstruction.
  - Dexamethasone may temporarily alleviate inflammation.

WHEN TO REFER

- Progressive or continuous stridor
- Poor weight gain or growth associated with persistent stridor
- Repeated hospitalization
- Presence of cutaneous hemangiomas in association with persistent stridor
- Severe episodes of stridor causing hypoxemia or cyanosis
- Laryngomalacia requiring surgical management to relieve the obstruction caused by redundant epiglottic folds or arytenoid tissue

WHEN TO ADMIT

- Respiratory distress or hypoxemia
- Inability to eat or drink
- Altered mental status or signs of fatigue
- Stridor associated with signs of increased intracranial pressure

DEFINITION

- The *Diagnostic and Statistical Manual of Mental Disorders,* 5th Edition (*DSM-5*) replaced the terms "substance abuse" and "substance dependence" with *substance use disorder* (SUD)—mild, moderate, or severe.
- Alcohol, marijuana, and tobacco are the most commonly used substances among youth.
- "Addiction" is not an official diagnostic term.
  - Refers to loss of control or obsessive use of a substance associated with neurologic changes in the brain's reward center.

HISTORY

- The American Academy of Pediatrics (AAP) recommends routinely screening every adolescent for substance use.
- Youth are identified for many reasons, including
  - Parents or teachers have expressed a concern about substance use.
  - The youth has physical signs or symptoms suggesting substance use.
  - Nonspecific symptoms suggesting substance use (eg, declining school performance or attendance, car crash, association with friends who are using substances).
  - Asymptomatic youth has a positive substance use screening test result.
- Pediatricians should include a psychosocial interview to assess
  - Family and peer relationships
  - Academic progress
  - Recreational activities
  - Sexual behavior
  - Drug use
- HEADSSS is an acronym that can help physicians to inquire about key domains
  - **H**ome
  - **E**ducation
  - **A**ctivities
  - **D**rugs
  - **S**afety
  - **S**exuality
  - **S**uicide or depression
- Previsit questionnaires are also available to capture this information.
- Risk factors, such as early initiation of use, family history of SUDs, and co-occurring mental health disorders, should be considered in the overall assessment.

PHYSICAL EXAMINATION

- A complete evaluation for an SUD includes a complete physical examination (**Table 1**).

DIFFERENTIAL DIAGNOSIS

- The new diagnostic classification is based on the number of criteria that are met.
  - 2–3 constitute a mild disorder.
  - 4–5, moderate.
  - ≥6, severe.
- Physical illness.
  - Drug or alcohol withdrawal may present as a physical illness and is potentially a medical emergency.
  - Psychiatric symptoms may be associated with medical illness (eg, encephalitis, cerebritis) and may be mistaken for drug intoxication.
- Assessment of patients in moderate-risk or high-risk category to determine problems associated with use and effects on functioning at home, at school, and with peers.
- Consider if the onset or acceleration of substance use was preceded by a distressing experience.
  - Physicians should speak separately and confidentially with the youth and parents to explore this possibility.
  - Parents are often unaware of exposures that children may have had at school or in the community and may underestimate the effect on children of major traumas in the family.
- Other anxiety disorders
  - Commonly co-occur with SUDs, and the relationship is bidirectional.
    - Anxious youth may be more likely to use substances.
    - Substance use may cause or precipitate anxiety disorders.
- Psychosis.
  - Though rare, onset of bipolar disorder or schizophrenia in late adolescence may be subtle and marked only by frightening hallucinations or delusions that the youth does not disclose.
  - Symptoms may result from the use of, precipitate the use of, or accelerate the use of substances.
- Attention-deficit/hyperactivity disorder (ADHD).
  - Adolescents with ADHD have higher rates of SUDs than peers.
  - Results of studies about stimulant treatment for adolescents with ADHD are inconclusive.
    - Some indicate lower risk of developing an SUD.

Table 1. Physical Findings Potentially Indicating Substance Use and Substance Use Disorder

	Acute Intoxication	Chronic Impairment	Drug(s) to Consider
General appearance	Altered mood, strange/ inappropriate behavior	Poor dress or hygiene	Any drug
Vital signs		Weight loss	Heroin, cocaine
	Hypertension	Hypertension	Cocaine, amphetamine
	Hypotension, hypothermia		Heroin
	Hyperthermia		Cocaine, amphetamine, ecstasy
	Tachycardia		Marijuana, cocaine, amphetamine
Ears, nose, and throat	Conjunctival injection		Marijuana, inhalants
	Dilated pupils		Cocaine, amphetamines
	Constricted pupils		Opioids
	Sluggish pupillary response		Barbiturates
		Nasal irritation	Cocaine, inhalants, opioids (if sniffing)
Cardiac	Arrhythmias	Arrhythmias	Methadone, cocaine, amphetamine
Chest		Gynecomastia	Marijuana, anabolic steroids
Genitourinary		Testicular atrophy, clitoromegaly	Anabolic steroids
Skin		Acne, hirsutism	Anabolic steroids
	Abscesses, needle track marks		IV drug use
Neurologic	Altered sensorium		Any substance
	Ataxia		Alcohol, barbiturates
	Nystagmus		Barbiturates
	Hyporeflexia or hyperreflexia		Marijuana, cocaine, amphetamine

Abbreviation: IV, intravenous.

- There is no evidence that stimulant treatment increases risk.

- Key details to assess in high-risk patients include
  - Alcohol: key historical elements
    - Age of first drunkenness
    - Frequency of drinking episodes
    - Typical amount of alcohol consumed
    - Greatest amount of alcohol consumed
    - History of blackouts, overdose, or emergency department visits
    - Problems associated with alcohol use
    - Quit attempts
  - Marijuana: key historical elements
    - Age at initiation
    - Frequency of marijuana use
    - History of paranoia or hallucinations
    - Problems associated with marijuana use
    - Quit attempts
- Conditions that may mimic or co-occur with substance use include
  - Learning problems or disabilities
    - Unidentified learning difficulties can contribute to frustration and stress, school failure, and association with peers who use substances.
  - Depression or bipolar disorder
    - Marked sleep disturbance, disturbed appetite, low mood, or tearfulness could indicate depression.
    - Symptoms of depression rapidly alternating with cycles of agitation may suggest bipolar mood disorder.
  - Exposure to adverse childhood experiences
    - Youth who have experienced or witnessed trauma
    - Violence
    - A natural disaster
    - Separation from a parent
    - Parental divorce or separation
    - Parental substance use
    - Neglect

LABORATORY EVALUATION

- Drug testing may be a useful part of a complete assessment for SUD, particularly when there is concern and the adolescent denies use.
  - Drug testing is a complex laboratory procedure with significant potential for false-positive and false-negative results.
- Should be used only as an adjunct to history and physical evaluation.
- Testing and sharing of results should only be done with the permission of the adolescent.
- If an adolescent refuses a test that is indicated, parents can be coached to implement logical consequences as they would in other circumstances.
- If there is concern for harm, the pediatrician should consider breaching confidentiality.

DIAGNOSTIC PROCEDURES

- Screening tools minimize the likelihood of missing substance use problems or disorders.
- Brief screens include
  - Screening to Brief Intervention
    - 2-question frequency screen
    - Screens for tobacco, alcohol, marijuana, and other illicit drug use
    - Discriminates between no use, no SUD, moderate SUD, and severe SUD, based on *DSM-5* diagnoses
  - Brief Screener for Tobacco, Alcohol, and Other Drugs
    - Identifies problematic tobacco, alcohol, and marijuana use in pediatric settings.
  - National Institute on Alcohol Abuse and Alcoholism youth alcohol screen
    - 2-question screen
    - Screens for friends' use and own use
- Brief assessments
  - CRAFFT (**c**ar, **r**elax, **a**lone, **f**riends/family, **f**orget, **t**rouble)
    - A good tool for quickly identifying problems associated with substance use
    - Not a diagnostic tool
  - Global Appraisal of Individual Needs
    - Assesses for SUDs and mental health disorders
  - Alcohol Use Disorders Identification Test
    - Assesses risky drinking
    - Not a diagnostic tool

TREATMENT APPROACH

- It is impossible to isolate youth with SUDs from substances.
  - Teach youths to identify high-risk situations, avoid them when possible, and avoid use even when confronted with others who are using.
  - Acknowledge and reinforce protective factors.
    - Good relationships with at least one parent or important adult
    - Prosocial peers
    - Concerned or caring family
    - Help seeking
    - Connection to positive organizations

- Consider the child's social environment.
- Questions to raise include
  - *Is an external problem (adverse experience such as abuse, bullying, or family socioeconomic stress) adding to stress?* Take steps to explore and reduce stressors, as feasible.
  - *Are peers using substances?*
- Explore options to increase healthy social and recreational activities and reduce contact with peers who are using substances.
  - Encourage youth to change their phone numbers and eliminate friends with whom they previously used drugs.
- Encourage healthy habits.
  - Exercise
  - Outdoor time
  - Healthy and consistent diet
  - Sleep (critically important to mental health)
  - Limited screen time
  - One-on-one time with parents
  - Time with peers who are not using substances
- Offer praise for positive behavior changes.
  - Acknowledge the youth's strengths.
  - Acknowledge challenges including new schools, new friends, new social circles, and new academic demands.
  - Acknowledge that while the youth's friends may be using substances heavily, most same-age peers do not.
- Encourage involvement in prosocial activities.
  - Youth development
  - Leadership
  - Volunteer
  - Sports teams, clubs
  - Mentoring
  - Faith-based programs
- Monitor progress.

SPECIFIC TREATMENT

- Counseling to reduce drug use and high-risk behaviors
  - Tailor intervention to stage of use (**Table 2**).
  - Depending on the screening tool used, levels of risk include
    - Abstinence
    - Lower risk (ie, use but no SUD)
    - Moderate risk (ie, mild or moderate SUD)
    - High risk (ie, youth with a severe SUD)
    - Acute risk
  - Some tools do not discriminate between moderate and high risk.
    - In these cases, assessment is used to identify severe SUD (ie, addiction) that will benefit most from referral to subspecialty care.
    - Use motivational interviewing techniques.

WHEN TO REFER

- Mild or moderate SUD indicates particularly hazardous use or problems associated with use.
  - No clear referral guidelines for adolescents with an SUD unless there is co-occurring mental illness.
  - Those with a mild SUD can likely be managed in primary care.
  - Moderate SUD may not require referral to subspecialty care, and decision can be left to the discretion of the primary care physician.
  - Severe SUD suggests that an individual would likely benefit from specialized treatment.
    - Many adolescents with a severe SUD will not accept a referral.
    - Primary care physicians should be prepared to manage these patients in primary care while trying to facilitate completion of the referral.
- The AAP statement on screening, brief intervention, and referral to treatment provides specific guidance for when to refer patients and to which level of care.
- Indications for specialty referral include
  - Child or adolescent <15 years with a positive screen result for moderate- or high-risk substance use.
  - Interventions by primary care physician have not reduced use.
  - Drug use is endangering the youth or others.
  - Drug use is threatening the achievement of developmentally important goals, such as school attendance and performance, or relationships.
  - Co-occurring mental health disorders are present.
  - Youth has a history of trauma.
  - Youth is using drugs other than alcohol, marijuana, or tobacco.
  - Parents are not involved or do not acknowledge concerns, or one or both parents have an active SUD.
- If the child is referred to a specialist, the family will probably need assistance with the requirements of their health insurance or the public mental health system and selecting an appropriate physician.

Table 2. Substance Use Spectrum and Goals for Office Intervention

Stage/Triage Category	Description	Office-Based Intervention Goals
Abstinence	No use of drugs or alcohol	**Positive Reinforcement** Prevent or delay initiation of substance use through positive reinforcement. Include statement about use norms, especially for younger children.
No SUD	Use of alcohol or marijuana with peers in relatively low-risk situations; without related problems or interference with domains of functioning, such as school, sports, hobbies, or home life.	**Brief Advice** Encourage cessation through brief medically based advice, particularly as it relates to patient's future goals. Promote patient strengths.
Mild/moderate SUD	As defined by *DSM-5* Adolescents with mild/moderate SUDs typically have associated problems or high-risk behaviors associated with use.	**Brief Motivational Intervention** Encourage cessation, even for a brief trial period, if patient is willing. Reduce potential harm by reducing use and focusing on highest-risk behaviors. Encourage parent involvement to help with follow-through. Follow up with primary care physician or allied mental health professional to continue conversation and harm reduction.
Severe SUD (addiction)	As defined in *DSM-5* Loss of control or compulsive drug use	**Brief motivational intervention** targeting referral into ongoing treatment Encourage reducing use and high-risk behaviors and engaging adolescent to accept a referral to treatment. Share diagnosis and referral information with parents, if possible. Follow-up by primary care physician to ensure compliance and encourage long-term treatment.
Acute risk	Use associated with acute risk of overdose or in a situation that is physically risky	**Intervention for safety** may include breaching confidentiality to inform parents about use and referral to treatment in a timely fashion. Verbal contracts not to use while awaiting a formal evaluation and advice to parents on how to monitor and what to do in case of escalation may also be helpful.

Abbreviations: *DSM-5, Diagnostic and Statistical Manual of Mental Disorders,* 5th Edition; SUD, substance use disorder.

American Academy of Pediatrics Committee on Substance Abuse. Substance use screening, brief intervention, and referral to treatment for pediatricians. *Pediatrics.* 2011;128(5):e1330–e1340.

- The primary care physician and specialist need to reach agreement on respective roles in care and establish a mechanism for communication.
- The primary care physician can
  - Encourage positive view of treatment.
  - Monitor progress in care and possible co-occurring disorders.
  - Coordinate care provided by parents, school, medical home, and specialists.
  - Encourage parents to seek treatment for tobacco use and other dependencies.
- Adolescents (and, in some cases, their parents) may resist treatment. In these cases, the following steps may be helpful:
  - If referral is clearly indicated, partner with parents to increase the likelihood of follow-through.
  - Clarify with the youth the relevant laws and protections for minors.
    - In many states, parents can file an order with police to help enforce house rules.
    - Depending on the situation, it may be necessary to involve child protection services.
  - Provide education and motivational counseling to reduce harm and improve functioning at home.
    - Even if unwilling to engage with specific substance use treatment, youth may be willing to see a licensed clinical social worker or psychologist.

FOLLOW-UP

- Following referral for specialty care, the AAP recommends that the physician remain involved with the child and family, supporting treatment, monitoring progress, and providing complementary primary care.

COMPLICATIONS

- Medical complications of chronic substance use, although sometimes severe, usually do not appear until after adolescence.
- Negative health effects may be related to direct consequences of substances or associated risky behaviors.

PROGNOSIS

- Substance use, even without symptoms that rise to the level of a disorder, is associated with significant health problems, including
  - Injuries
  - Accidents
  - Unintentional sexual activity
  - Sexually transmitted infections

PREVENTION

- Primary care physicians should provide youth who are not using substances or are lower risk with positive encouragement about smart and healthy choices.
- Primary care physicians should include a discussion of the risks of impaired driving and help the adolescent plan for times when a driver may have used alcohol or drugs.
  - Students Against Destructive Decisions has a helpful framework for physicians to use with patients and parents for driving safety.

Sudden Unexpected Infant Death

DEFINITION

- Sudden unexpected infant death (SUID).
  - Also sometimes referred to as sudden unexpected death in infancy, or SUDI
- Refers to all causes of death during infancy that occur suddenly and unexpectedly.
  - Sudden infant death syndrome (SIDS)
  - Accidental injuries (eg, suffocation, strangulation, entrapment)
- SIDS is the sudden death of an infant <1 year that remains unexplained after thorough investigation, including
  - Performance of complete autopsy
  - Examination of death scene
  - Review of clinical history
  - Diagnosis of exclusion
- Cause of most SUID deaths is undetermined
  - Cause of death cannot be definitively ascertained; for instance, autopsy findings are consistent with SIDS, but sleep circumstances suggest that suffocation is a possibility.

DIFFERENTIAL DIAGNOSIS

- Illnesses that should be considered in the differential diagnosis include
  - Sepsis
  - Pneumonia
  - Myocarditis
  - Cardiomyopathy
  - Congenital heart defect
  - Arrhythmia
  - Prolonged QT syndrome
  - Trauma (accidental or non-accidental)
  - Suffocation
  - Adrenal hypoplasia
  - Inherited metabolic disorders, such as fatty acid oxidation disorders
- The large majority of SIDS cases have no evidence suggesting parental psychiatric disease or neglect of the infant.
- The proportion of SIDS deaths attributable to homicide probably is <10%.
- Suffocation, accidental or non-accidental, is difficult to distinguish on autopsy from SIDS.
  - Since 1999, some deaths that would previously have been classified as SIDS are now being classified as suffocation.

DIAGNOSTIC APPROACH

- SIDS is a diagnosis of exclusion.
- Other conditions must be ruled out by autopsy, death scene investigation, and review of the clinical history.

TREATMENT APPROACH

- SIDS risk reduction has centered on eliminating risk factors.

SPECIFIC TREATMENTS

- The American Academy of Pediatrics has made the following recommendations for SIDS and SUID risk reduction:
  - Infants should be placed in a supine position for every sleep.
    - — Side sleeping is not advised.
  - Firm crib mattress.
  - Well-fitted sheet.
  - Soft materials or objects, such as pillows, quilts, comforters, sheepskins, and stuffed toys, should be kept out of the infant's sleeping environment.
  - Loose bedding, such as blankets and sheets, should be avoided.
  - Smoking during pregnancy or in the infant's environment is strongly discouraged.
  - A separate but proximate sleeping environment is recommended.
- Offering a pacifier at nap time and bedtime should be considered.
  - Does not need to be reinserted once the infant falls asleep; should not be forced if the infant refuses it.
  - Delay use of pacifier in breastfeeding infants until 1 month of age to ensure that breastfeeding is fully established.
  - Do not use pacifiers with attached strings or elastic for sleeping infants.
- Avoid overheating and head covering during sleep.
- Commercial devices marketed to reduce risk of SIDS should not be used.
- Home monitors should not be used as a strategy to reduce risk of SIDS.

FOLLOW-UP

- Loss of an infant to SIDS is devastating for the family, friends, and health care professionals.
  - Uncertainty as to cause of death adds additional difficulty to the grief process.

- Physician can play an active role by
  - Ensuring that an autopsy is performed in all cases of sudden unexpected death
  - Discussing results of the autopsy with parents
  - Providing emotional support to the entire family, including age-appropriate support for surviving siblings
- The family should be directed to local counseling and support groups.

COMPLICATIONS

- With the increased rate of supine sleeping, the incidence of plagiocephaly without synostosis has increased.
  - Infants with plagiocephaly are
    - More likely not to have had head position altered when put down to sleep
    - More likely to have spent little awake time in the prone position ("tummy time")
    - Less likely to have been held in the upright position while awake
- Development of positional plagiocephaly can be avoided by
  - Altering supine head position during sleep
  - Encouraging upright cuddle time
  - Avoiding excessive time in car safety seats, carriers, and bouncers, which place pressure on the occiput
  - Encouraging tummy time when the infant is awake and observed
    - Awake tummy time will also enhance upper body motor development.
- A perception exists that sleeping supine may increase the risk of
  - Gastroesophageal reflux
  - Choking
  - Aspiration
- Evidence indicates that infants who vomit are at greater risk of choking when they are prone.
- Incidence of aspiration or vomiting has not increased with increased supine sleeping.

PREVENTION

- Sleeping in a non-prone position
  - The rate of prone sleeping decreased from 70% to 13.5% in 2010.
  - The rate of SIDS decreased from 1.2 deaths per 1,000 live births to 0.42 deaths per 1,000 live births in 2012.
  - Similar decreases in SIDS have been experienced in other countries that have initiated similar educational campaigns.
- Use of pacifiers
  - By a yet-unidentified mechanism, pacifiers appear to reduce the risk of SIDS when used at sleep time.
  - 2 recent meta-analyses demonstrate a strong protective effect.
  - Several studies have shown a negative correlation between pacifier use and breastfeeding duration.
    - Early pacifier use may interfere with establishment of good breastfeeding practices.
    - Pacifiers should not be offered for the first month of life until breastfeeding has been well established.
  - Infants with gastroesophageal reflux should be placed for sleep in the supine position.
    - The rare exception is in infants with upper airway disorders for whom airway protective mechanisms are impaired and risk for death from gastroesophageal reflux is greater than risk for SIDS.

Symptoms of Emotional Disturbance in Young Children (Birth to 5 Years)

DEFINITION

- The full range of behavioral difficulties, emotional disturbances, and relationship difficulties that may occur in early childhood, especially in the context of adverse childhood experiences.
- Associated adverse outcomes, including child and family suffering, school failure, mental and physical illnesses, and fractured social networks, may continue throughout the life span.

HISTORY

- Symptoms and clinical findings suggesting social-emotional problems must be differentiated from typical behavior.
- Chronic or significant medical problems may lead to
  - Developmental delays
  - Behavior problems
- Concerns about child's behavior or emotions.
  - Regulatory difficulties evidenced by difficulty calming, irregular sleep or feeding patterns, excessive sensitivity to sensory experiences
  - Difficulty organizing behaviors and extreme aggression or severe or persistent tantrums that involve injury or damage to objects
  - Significant difficulty adjusting to or expulsion from child care or preschool
  - Activity and impulsivity levels excessive for developmental age
  - Unhappy mood, irritability, lack of true joy
  - Anxiety, especially related to specific triggers or traumatic reminders, separation from caregiver, or experiencing new situations
  - Unwillingness to talk in public, even with reassurance
  - Excessively rigid behavioral patterns or habits that interfere with typical functioning
- Concerns about caregiver.
  - Inability to consider child's strengths, disorganized when talking about the child, talks about the child only in a negative tone
  - No anticipation of child's need for comfort and does not offer appropriate comfort in new situations or times of distress
  - Excessive protection of child, developmentally appropriate exploration not allowed
  - Abuse or neglect (involvement with child protection)
- Concerns about relationship.
  - Child does not elicit comfort or reassurance from caregiver in times of distress.
  - Child (>9 months' developmental age) does not look to caregiver in novel situations or to share joy or excitement.
  - Child does not manifest age-appropriate stranger anxiety.
  - Child has not met appropriate social milestones for social reciprocity, peer interactions, adult interactions, or focused attachment (comfort-seeking) behaviors with primary caregiver.
  - Child's relationship with caregiver has been disrupted.
- Risk factors for increased susceptibility.
  - History of maltreatment or significant caregiving disruption
  - Family stressors
  - History of adverse childhood experience in parents
  - Parental substance abuse, mental illness, or domestic violence

DIFFERENTIAL DIAGNOSIS

- Extreme response to normal limits, fatigue, hunger, or new situations are part of typical development in third and fourth years of life.
- Cognitive and language difficulties.
  - Child may experience frustration expressing needs and desires.
  - Children with intellectual disabilities usually function at a level younger than chronological age and size.
- Hearing or vision problems.
  - Screen for sensory deficits in all children manifesting atypical development or behavior.
- Autism spectrum disorder.
  - Problems with social relatedness
  - Delay of expressive language or unusual syntax or porosity
  - Limited range of interest with persistent and intense interest in a particular activity or subject
  - Atypical mannerisms that interfere with normal function
  - Rigid expectation for routine with anxiety or anger if not met
  - Higher than usual risk for comorbid psychiatric disorders

- Sleep problems or feeding disorders.
  - Sleep deprivation as a result of bedtime struggles, night waking, or obstructive sleep apnea
    - Note that social-emotional problems can cause sleep difficulties.
  - Food refusal or overeating
    - Can result in escalating cycle with parental distress around eating pattern
- Attention-deficit/hyperactivity disorder (ADHD).
  - High impulsivity, inattentiveness, distractibility
  - Important to observe whether symptoms occur in multiple settings (required for ADHD)
  - Must be distinguished from developmentally inappropriate expectations and from parental symptoms, such as depression
  - May be confused with lead toxicity or medications such as steroids or sympathomimetics
- Disruptive behavior disorders (oppositional defiant disorder, conduct disorder).
  - Most commonly occur with inconsistent or coercive caregiving environment
- Sadness and irritability.
  - Consider major depressive disorder in children with extreme sadness or irritability.
  - Associated symptoms: sleep and appetite changes, play or talk centered around death and dying, decreased joy in play, difficulty concentrating.
  - Diagnosis of bipolar disorder in preschool children has not been established.
- Anxiety disorders.
  - General anxiety, extreme separation anxiety, school avoidance behaviors, selective mutism—all are often accompanied by extreme distress in the face of the trigger.
  - Young children with obsessive-compulsive behaviors may present with behavioral symptoms when asked to interrupt a compulsive behavior.
- Trauma-related symptoms.
  - Similar to presentation of posttraumatic stress disorder seen in older children.
  - Reexperience trauma in thoughts, speech, play, dreams.
  - Emotional and physiologic hyperarousal to reminders of trauma.
  - Avoidance of reminders of the trauma.
  - Numbing symptoms.
- Parental mental health problems, substance abuse, severe cognitive limitations.
  - Unpredictable or inconsistent parenting, especially if neglectful or leading to dangerous experiences.
  - Consider in children with a history of foster care or adoption.
  - Depression, other mental illness, bereavement, substance abuse, cognitive disability, or socioeconomic disadvantage may prevent caregiver from nurturing effectively.
- Disordered attachment or parent-child relationship difficulty.
  - Bond can be affected by characteristics of child or caregiver.
  - Suboptimal relationship may manifest as ineffective or inconsistent soothing, nurturing, or disciplinary behaviors by caregiver or lack of responsiveness by the child.
  - Parental history of unsafe relationships may affect parent's view or experience of the relationship.
  - May present as
    - Parent who experiences needs of the child as excessive or troublesome
    - Child who develops maladaptive ways of engaging parent's attention
    - Child who does not make attempts to engage parent

DIAGNOSTIC PROCEDURES

- Psychosocial screening instruments (**Table 1**)
  - Negative results indicate child is within lower-risk group but should not override physician's concerns based on history or observations.
  - Positive results may indicate a mental health problem, extreme parental distress, or a problem with parent-child relationship.

TREATMENT APPROACH

- Recognize and reinforce strengths of the child and family.
- Acknowledge distress of the social-emotional concern.
- Ensure safety from
  - Family partner violence, child abuse, community violence
  - Unsafe housing
  - Access to dangerous medications
- Address basic needs, such as housing, child care, food, and shelter.
- Support parent mental health.
- Reframe child's behaviors to allow parents to experience them differently.
- Explore opportunities for positive parent-child interactions.
- Encourage healthy habits and activities.
- Offer initial interventions.

Table 1. General Psychosocial Screening Results Suggesting Social-Emotional Problems

Screening Area	Screening Instrument	Score
Child	Baby Pediatric Symptom Checklist (BPSC) (irritability, inflexibility, difficulties in parenting)	A score of ≥3 is considered positive.
	Preschool PSC (internalizing, externalizing, attention, and parenting challenges)	A score of ≥9 is considered positive.
	Early Childhood Screening Assessment (assesses emotional and behavioral development in young children 18–60 months and maternal distress)	A score of ≥18 on items 1–36 indicates a higher than usual risk of disorder. A score of ≥1 on item 39 or 40 suggests risk of caregiver depression.
	Ages & Stages Questionnaire: Social-Emotional 2 (ASQ:SE-2) (useful as early as 4 months to screen for problems in caregiver-infant bond and interaction)	Each measure includes specific instructions about cutoff score for that age.
Environment	Edinburgh Postpartum Depression Scale	Score of ≥12 is considered positive.
	Patient Health Questionnaire-2	Any positive response is considered positive.
	Abuse assessment screen	Positive response to any question indicates high risk of interpersonal violence.
	Multidimensional Scale of Perceived Social Support (MSPSS)	Positive responses suggest high levels of stress associated with parenting and low level of social support.
	Caregiver Strain Questionnaire	Score of ≥7 suggests high level of caregiver strain.
	Bright Futures questionnaires	Answers suggest social-emotional stressors.
	Parenting stress index	Results suggest high levels of stress associated with parenting or within the parent-child relationship.

- Provide resources.
- Monitor progress.

SPECIFIC TREATMENT

Strategies for Building Social-Emotional Skills and Resilience

- Promote daily positive activities between parent and child.
  - Enlist extended family, friends, or involved agency to alleviate parental stresses and provide emotional support.
  - Educate about the importance of smiling with young infants, cooing with older infants, attending to vocalization or speech, and reading and playing at all ages.
  - Assist with recognizing the child's cues.
  - Increase parent's one-on-one time with child (eg, through daily routines at mealtime or bedtime).
  - Build resilience with anticipatory guidance from *Bright Futures Guidelines* and by emphasizing individual strengths.

- Apply positive parenting principles to toddlers and preschoolers.
  - Reinforce desired behaviors using parental attention.
  - Help child develop emotional vocabulary.
  - Encourage praise and rewards for specific, agreed-on behaviors.
  - "Pick battles" and focus discipline on priority areas.
  - Reduce positive reinforcement of disruptive behavior.
  - Teach recognition of the child's anxiety, to expose child only to manageable anxiety-provoking situations, to provide support and praise for managing feelings.
  - When possible, reorganize child's day to avoid situations in which the child cannot maintain control.
  - Ask other care providers to apply similar principles.
- Encourage parents to be calm and consistent.
  - Set clear house rules and give short, specific commands about desired behavior (not prohibitions about undesired behavior).
  - Provide consequences for misbehavior that are not drastic or overlong.
  - Find a way for children to make reparations for negative behavior.
  - Avoid arguments or explanations when enforcing a rule; defer negotiations until periods of calm.
  - Consider parenting classes.

Evidence-Based Programs

- Parenting programs for disruptive behavioral problems
  - The Incredible Years
  - Triple P Positive Parenting Program
  - Parent-Child Interaction Therapy
- Programs for high-risk pregnant women (first-time mother, refer <28 weeks' gestation)
  - Nurse-Family Partnership
- Programs for children in foster care
  - Attachment and Biobehavioral Catch-up
  - Treatment Foster Care Oregon
  - Parent-Child Interaction Therapy
- Programs for parent-child relationship disturbances and high-risk parenting situations
  - Circle of Security
  - Promoting First Relationships
  - Parents as Teachers
  - Child-Parent Psychotherapy
- Programs for children exposed to trauma, including sexual abuse or domestic violence
  - Cognitive behavioral therapy
- Psychopharmacologic interventions
  - Minimal evidence to support medication in this age group

WHEN TO REFER

- Involve specialists
  - When child <5 years has symptoms of social-emotional problems causing functional impairment or distress, such as
    - Symptoms of anxiety, sadness, or irritability that limit participation in family interactions, child care experiences, or other normative experiences
    - Disruptive behaviors in or out of home that limit participation in developmentally appropriate experiences
    - Ineffective use of caregiver for emotional support; lack of selectiveness in social interactions with strangers
    - Sleep or eating problems unresponsive to primary care interventions
  - When parent is
    - Very negative toward child
    - Compromised by physical or mental illness
    - Disengaged or inconsistent in providing nurturing
    - Unresponsive to primary care guidance
  - When parent has difficulty allowing child to have developmentally appropriate opportunities for exploration.
  - When family is not able to maintain calm, consistent, safe environment, consider reporting to child protective services.

PREVENTION

- Child's relationship with caring, nurturing adults is most critical factor in development of resilience to normative stresses of childhood.
- Interventions that support development of positive parent-child interactions positively influence brain development, intelligence, and central nervous system hormonal patterns.
- Pro-social behaviors and emotional regulation are supported by
  - Modeling and reinforcing behavior
  - Helping child organize emotions in response to challenging situations

Syncope

DEFINITION

- Syncope: a transient sudden loss of consciousness and postural tone
- Presyncope: the presence of sensory and postural impairment without actual loss of consciousness

HISTORY

- Detailed inquiry into exact circumstances surrounding the event.
  - Time of day
  - Presence of upper respiratory infection
  - Time since last meal
  - Posture during syncope and time spent in this posture before syncope
  - Presence of prodromal symptoms
  - Duration of loss of consciousness
    - Consciousness usually is regained quickly in the case of vasovagal syncope (a few seconds to 1 or 2 minutes).
    - A seizure may last longer, and the postictal state may be characterized by prolonged confusion and fatigue.
  - Bystander testimony
    - In orthostatic hypotension, symptoms occur within seconds of standing; in neurally mediated syncope (NMS), symptoms characteristically appear after being upright for at least a few minutes.
  - Any headache or prolonged disorientation after syncope
  - Circumstances precipitating the event
    - The prodrome of a seizure may consist of an aura; a cardiac event often occurs without warning or is induced by exercise.
    - NMS is most often brought about by pain or prolonged standing, especially in warm environments.
  - Degree of unconsciousness
    - Was the child completely unconscious?
    - Was some degree of responsiveness present, suggesting hysteria or malingering?
      - A truly unconscious person will not respond if the eyelashes are lightly brushed.
      - A hysterical person will respond, albeit often with just a mild flickering of the lids.
    - In NMS of childhood, loss of consciousness typically is preceded by
      - Light-headedness, nausea, yawning, feeling of being hot, sounds seeming distant
  - The presence of seizure-like movements
    - However, generalized tonic-clonic movements may be seen in any form of syncope.
- Significant diseases in the medical history include
  - Congenital heart disease
  - Seizure disorder
  - Endocrine abnormality, such as diabetes
- Migraine.
  - The primary care physician should always ask about migraine when a syncopal episode does not fit the typical pattern of NMS, particularly if dizziness occurs in the sitting position and no other provoking factors can be elicited.
  - History of flashing lights, severe headache preceding syncope, and family history of migraines usually help clinch the diagnosis of migraine.
- Recurrent syncopal episodes are unusual and may require more extensive testing.
- Family history.
  - Seizure disorders and cardiac disease leading to syncope may be inherited in an autosomal-dominant fashion.
    - Marfan syndrome
    - Hypertrophic cardiomyopathy
    - Prolonged QT syndrome
  - Breath-holding spells also can have a familial pattern.
- Occasionally, a cause is not identifiable.

PHYSICAL EXAMINATION

- Level of consciousness
  - A child who is not alert and oriented
    - Has not had a benign syncopal episode
    - Needs immediate evaluation for potentially life-threatening causes
  - In most children who are fully alert after a syncopal episode, physical examination is normal.
- Heart
  - Cardiac murmur may point to an obstructive lesion, such as aortic or pulmonic stenosis.
  - Listening to the heart in the supine and upright positions is important.
    - A mild obstructive gradient in hypertrophic cardiomyopathy may become audible only when the patient is upright.
  - Heart rate and blood pressure.
    - Obtain in the supine and upright positions to ascertain the presence of orthostatic intolerance.

DIFFERENTIAL DIAGNOSIS

Behavioral or Psychiatric Causes

- Breath-holding spells
  - Two types of breath-holding spells typically occur in children between 6 months and 3 years.
    - Cyanotic
      - Cyanosis and apnea are precipitated after a child is upset and begins to cry.
      - Stiffening of the body and loss of consciousness may soon follow.
      - The pathophysiologic basis is unclear, but crying during expiration may cause increased intrathoracic pressure, which leads to low cardiac output.
      - Hypoxia combined with decreased cerebral blood flow leads to loss of consciousness.
      - The event is brief, and afterward, the child becomes fully conscious.
    - Pallid
      - Pallid breath-holding spells (pallid infantile syncope) are less common and usually begin with sudden pain.
      - The child suddenly becomes pale and limp and loses consciousness.
      - The pathophysiologic basis is increased vagal tone causing apparent asystole.
      - Ordinarily lasts only seconds to minutes, and the child awakens to full consciousness.
- Hyperventilation
  - Benign.
  - Frequent among adolescents, especially in the presence of anxiety.
  - It results in the washing out of carbon dioxide, and hypocapnia causes reduced cerebral blood flow, dizziness, and syncope.
  - Classically, hyperventilation is associated with numbness and paresthesias of the hands and feet.
- Psychiatric syncope
  - The child is likely to be unusually calm.
  - No autonomic effects, such as change in heart rate or blood pressure, are noted during episodes.
  - Episodes tend to be recurrent and frequent and to occur in front of an audience.
  - Recovery of consciousness often is prolonged, and usually no injury is sustained.

Cardiac Causes

- Syncope can result from low cardiac output secondary to a dysrhythmia or a structural problem.
- The abnormal rhythm underlying the syncope may be too slow or too fast.
- Bradycardia.
  - Sick sinus syndrome is extremely rare in a child with a typical heart.
    - Usually seen after extensive surgery in the atria with the Senning and Mustard operations for transposition of the great arteries.
    - Patients who have undergone the Fontan procedure for a single ventricle may be at risk secondary to atriotomies and dilated atria.
  - Atrioventricular (AV) block.
    - Very slow heart rates from AV block can lead to syncopal episodes termed *Adams-Stokes attacks.*
    - Congenital AV block in the presence of a structurally typical heart is most commonly associated with a mother who has a history of systemic lupus erythematosus.
    - Structural heart disease most commonly associated with congenital AV block or risk of acquired AV block is corrected transposition of the great arteries.
    - AV block is also occasionally acquired after cardiac surgery or Lyme disease.
- Tachycardia.
  - Supraventricular tachycardia
    - Most children with supraventricular tachycardia have a structurally typical heart.
      - In those children, palpitations and dizziness are more common symptoms of supraventricular tachycardia than syncope.
    - With a structural abnormality resulting in reduced hemodynamic reserve (eg, a single ventricle), syncope may be a presenting feature.
    - In patients with congenital heart defects, Wolff-Parkinson-White syndrome is seen most often in children with disorders of the AV fibrous valve annuli, such as Ebstein anomaly and corrected transposition of the great arteries.
  - Ventricular tachycardia (VT)
    - Rare in children, but can cause sudden death.
    - Early identification of underlying conditions that predispose to VT can be lifesaving.
    - Prolonged QT syndrome.
      - Patients are at risk of sudden death secondary to a polymorphic VT termed *torsades de pointes.*
      - Prolongation of the QT interval may be part of a congenital syndrome.

- Two syndromes that result in prolonged QT interval are caused by mutations in genes encoding cardiac ion channels.
  - Romano-Ward syndrome: autosomal dominant
  - Jervell and Lange-Nielsen syndrome: autosomal recessive, associated with congenital neural deafness
- May be caused by an electrolyte imbalance, such as
  - Hypokalemia
  - Hypocalcemia
- May be caused by a variety of drugs, including
  - Tricyclic antidepressants
  - Certain macrolide antibiotics
  - Antiarrhythmic medications

— VT also can occur in children as a complication of myocarditis or in adolescents with tetralogy of Fallot who have undergone surgical repair in infancy.

- Pacemaker malfunction.
  - Syncope in a child with a pacemaker should prompt immediate interrogation of the device for a malfunction or inappropriate programming.
- Structural heart disease.
  - Acute reduction in cardiac output can result in reduced cerebral perfusion and syncope.
  - With certain heart conditions, patients may be able to maintain adequate cardiac output at rest but experience syncopal episodes with exercise.
  - Aortic stenosis.
    — Mechanisms that may contribute to syncope in children with severe aortic stenosis include
    - Impediment to the forward flow of blood from marked left ventricular hypertrophy
    - Stimulation of the ventricular mechanoreceptors, resulting in systemic vasodilatation
    - Subendocardial ischemia causing a ventricular arrhythmia
  - Hypertrophic cardiomyopathy.
    — Syncope with exercise may be an important presenting sign.
    — Most affected patients have no left ventricular obstruction at rest.
    - With exercise, they can develop a dynamic gradient with an acute reduction in cardiac output.
    - These patients also may develop VT from subendocardial ischemia.

    — The electrocardiogram often is abnormal.
    — The echocardiogram is diagnostic.
  - Tetralogy of Fallot.
    — Children with unrepaired tetralogy of Fallot may have syncopal episodes in association with hypercyanotic tet spells.
    — Syncope is often precipitated by crying, straining with a bowel movement, or awakening from sleep.
- Pulmonary hypertension.
  - With exertion, children with pulmonary hypertension may experience syncope from an inability to maintain transpulmonary flow.
- Marfan syndrome.
- Coronary artery abnormalities.
  - A patient with syncope who is demonstrated to have a coronary artery aberrant in its origin or course should be presumed at risk for sudden death.
  - Typically, syncope occurs with exercise.
  - Acquired abnormalities of the coronary arteries include
    — Coronary artery aneurysms
    — Stenosis caused by Kawasaki disease in early childhood.
  - Cocaine
    — Can cause acute coronary vasoconstriction and ventricular arrhythmias, with consequent syncope

Orthostatic Hypotension

- Symptoms of weakness and light-headedness develop, typically within seconds of standing.
- The sinus tachycardia of orthostatic hypotension sets this type of syncope apart from neurocardiogenic (vasovagal) syncope, during which bradycardia is a prominent sign.
- Volume depletion from any cause (in children, most commonly vomiting and diarrhea) exacerbates orthostasis.
- Drugs that cause vasodilation and diuretics can also stimulate orthostasis.
- Pregnancy should always be considered when a woman of childbearing age faints.
  - Increased estrogen and progesterone levels cause decreased peripheral vascular resistance and hypotension.
- Postural orthostasis tachycardia syndrome has been described within the last few years.
  - Diagnosis requires
    — Orthostatic heart rate acceleration >120 beats per minute (bpm) *or*
    — Absolute increase ≥30 bpm in the absence of significant orthostatic hypotension

- Two forms have been identified, both more common in young women.
  - Peripheral variety (more common)
    - Persistent tachycardia, associated with fatigue, exercise intolerance, and palpitations, is present while the patient is upright.
    - Onset may occur after a viral illness, trauma, or surgery.
  - β-Hypersensitivity (or central) form
    - Often associated with migraines, tremor, and excessive sweating

- Familial dysautonomia.
  - An inherited autosomal-recessive condition with abnormalities of the autonomic nervous system.
  - A rare but serious cause of orthostatic syncope.
  - Affected patients are at risk for sudden death.

NMS (Neurocardiogenic or Vasovagal Syncope)

- The most common form of syncope
- Also known as *common faint, church faint,* and *reflex syncope*
- Classified into 3 types.
  - Postural syncope
    - The most common type of NMS
    - Associated with the upright position, typically developing while the person is standing or walking
  - Central syncope
    - Occurs in response to strong emotional stimulation, such as pain, anticipated pain, or the sight of blood.
    - In susceptible individuals, emotional stimulation can trigger sympathetic inhibition and parasympathetic activation.
  - Situational syncope
    - Occurs after the specific stimulation of sensory or visceral afferents.
      - Syncope evoked by the hypersensitivity of carotid baroreceptors
      - Micturition syncope
      - Defecation syncope
      - Hair-grooming syncope
      - Swallow syncope
      - Cough syncope
      - Weight lifter syncope
    - All have been described in teenagers but are less common than in adults.

Neurologic Causes

- Seizures
  - Typically, generalized seizures are preceded by a prodrome that includes tonic-clonic activity with loss of consciousness and a period of confusion and lethargy after recovery.
  - Atypical seizures can be difficult to differentiate from the benign forms of syncope.
  - Loss of consciousness in the recumbent position is more likely to occur from seizure, especially if the heart is normal.
  - Pallor is seen more often in benign syncope, and flushing is more common with seizures.
  - Bowel incontinence points toward a seizure disorder.
- Migraine
  - Migraine should be considered in a child who has a syncopal episode that does not fit the pattern of typical NMS.
  - A history of flashing lights, severe headache preceding the episode of syncope, and a family history of migraines usually help clinch the diagnosis.
- Head trauma
  - Brief loss of consciousness with head trauma is not uncommon and is termed *concussion*.
- Narcolepsy

Metabolic Causes

- Hypoglycemia can cause syncope, most commonly in a child who has diabetes and is on medication.
  - Presyncopal symptoms may be present: weakness, hunger, confusion.
  - This syncope typically is not brief.
- Dehydration.
- Severe anemia.

Drug-Induced Syncope

- Diuretics
- Vasodilators

LABORATORY EVALUATION

- The complete blood cell count should be checked if anemia is suspected as the cause for syncope.
- Serum glucose should be checked if hypoglycemia is considered to be a cause of syncope.

IMAGING

- Echocardiography
  - When suspicion exists based on history (eg, syncope with exercise) or on examination of a structural cardiac lesion

- Usually can demonstrate the origin and course of the coronary arteries adequately

DIAGNOSTIC PROCEDURES

- Electrocardiography
  - The only test indicated in most patients with a history typical of benign syncope.
  - May reveal the presence of AV block or dysrhythmia.
  - Abnormally large left ventricular forces, especially with left ventricular strain, may be the only evidence of hypertrophic cardiomyopathy in a patient with typical findings on physical examination.
  - Corrected QT interval should be measured in all children with syncope or seizures to ensure that prolonged QT syndrome is not missed.
- Monitors
  - Holter monitor
    - 24-hour electrocardiographic monitoring test
    - Used if a cardiac dysrhythmia is strongly suspected because of
      - Prominent palpitations that occurred before the episode
      - History of cardiac surgery that may predispose a child to abnormal rhythms
  - Event monitor
    - Patients can keep the monitor for 1 month and use it when symptoms are occurring.
- Electrophysiologic testing and cardiac catheterization
  - Must be considered for any patient who has had syncope during active exercise and no abnormality on physical examination, electrocardiogram, and echocardiogram.
- Tilt table testing
  - Creates an orthostatic stress.
  - Can provoke symptoms in patients with NMS and orthostatic hypotension.
  - A means of provoking vasodepressor syncope in susceptible individuals after other, more serious causes have been ruled out.
  - Procedure.
    - The patient is placed supine on a table that has a footboard.
    - The table is then tilted up 60°–80° for 30–60 minutes.
    - Patients are monitored closely for a syncopal episode.
  - Sensitivity and specificity.
    - Sensitivity ranges from 30%–80%, depending on the laboratory.
    - Some centers use low-dose intravenous isoproterenol infusions to increase sensitivity.
    - The specificity of a negative test result without isoproterenol ranges from 80%–100%.
  - The utility of head-upright tilt table testing in children is still controversial.
  - Indications for the use of this test include
    - ≥3 syncopal episodes during a 12-month period with no evidence of heart disease
    - Syncope during exertion in which heart disease has been ruled out after an exhaustive workup
    - Recurrent syncopal episodes thought to be hysterical in nature

TREATMENT APPROACH

- The management of cardiac, neurologic, metabolic, and behavioral/psychiatric syncope depends on the cause.
- For most patients with NMS or orthostatic hypotension
  - Reassurance.
  - Education about the cause of the syncope and how to avoid aggravating factors, such as extreme heat or standing still for long periods.
  - Patients should be instructed to sit or lie down at the onset of any prodromal symptoms to avoid injury.

SPECIFIC TREATMENT

Isometric Exercises

- In a small randomized trial of adults, intense gripping of hands and tensing of the arms for 2 minutes at the onset of tilt-induced symptoms increased systolic blood pressure.
  - Syncope occurred in 37% of these patients, compared with 89% in those who did not perform the maneuver.
- "Tilt training"
  - Controversial, but may be helpful to some patients.
  - Patients are instructed to stand with their backs against a wall, initially for short periods, and slowly increasing the duration to ~30 minutes per day.

Volume Expansion

- A reduced frequency of syncope in adolescents with neurocardiogenic syncope was reported after they drank 2 L of water in the morning.
- Fludrocortisone is a synthetic mineralocorticoid that causes salt retention and expansion of the central blood volume.
  - One randomized trial in adolescents showed similar results to atenolol, but no placebo was studied.

β-Blockers

- Have been used for many years as therapy for neurocardiogenic syncope.
- Studies of their effectiveness have been, at best, equivocal.

Investigational Agents

- Midodrine
  - A direct α_1-receptor agonist that has been shown to reduce episodes in adults with severely symptomatic neurocardiogenic syncope
- Selective serotonin reuptake inhibitors (SSRIs)
  - Serotonin may have a role in regulating the sympathetic nervous system activity.
  - SSRIs have been considered for treatment of NMS.
- Paroxetine
  - In a trial in adults, has been shown to be superior to placebo
- Cardiac pacing
  - Currently has a very limited role in the management of syncope
  - Has been used for children in whom asystole is the prominent symptom in recurrent syncope caused by vagal hypertonia, including some patients with deglutition syncope

WHEN TO REFER

- Patient history of cardiac disease
- Family history of sudden death, cardiac disease, or deafness
- Recurrent episodes
- Recumbent episode
- Exertional syncope
- Prolonged loss of consciousness
- Associated chest pain or palpitations
- On medications that can alter cardiac conduction

FOLLOW-UP

- All patients with syncope need a close follow-up to monitor the frequency of syncopal episodes and also to monitor the response to therapy.

COMPLICATIONS

- Injury due to fall

PREVENTION

- Prognosis for syncope depends on its cause.

Temper Tantrums and Breath-Holding Spells

DEFINITION

- Temper tantrums and breath-holding spells are usually benign forms of childhood behavior evolving from preverbal attempts to express feelings of frustration and anger.

Tantrums

- A problem behavior rather than a behavioral problem

Breath-Holding Spells

- Cyanotic
  - Precipitated more often by anger or frustration than by fear or injury.
  - Child emits a short, loud cry; takes a deep breath; and holds it.
  - Cyanosis occurs after ~30 seconds.
- Pallid
  - More often precipitated by fear or minor injury.
  - Initial cry is brief or silent.
  - Spell then proceeds as with a cyanotic spell.

HISTORY

Temper Tantrums

- Tantrums are normal behavior, but several factors may suggest that further professional intervention is advisable.
  - Obtain a detailed history (ABCs).
    - **A**ntecedent: circumstances in which tantrums take place
    - **B**ehavior: specific description of tantrums
    - **C**onsequence: what happens following a tantrum
- Possible causes of persistent negativism or tantrums include
  - Too-restrictive parenting
  - Too little positive reinforcement and affection
  - Unreasonable behavioral expectations
- One study defined severe temper tantrums as "episodes of shouting, banging, kicking, or screaming occurring 3 or more times a day or lasting more than 15 minutes."
  - ~50% of these children had behavior problems.
  - Severe tantrums were associated with specific psychosocial issues (maternal depression, use of corporal punishment, marital stress, and low maternal education).
- Children who display tantrums regularly >5–6 years may have depression or poor self-esteem or live with a family that has emotional problems.
- When temper tantrums regularly occur at school, suspect academic problems because peer pressure usually inhibits displays of tantrums.
- Children exhibiting persistent tantrums along with other associated behaviors (eg, inability to concentrate, stereotypical behaviors, unrealistic fears, inability to display affection) may have more significant underlying problems.
  - Attention-deficit/hyperactivity disorder
  - Oppositional defiant disorder
  - Autism spectrum disorder

Breath-Holding Spells

- A positive family history occurs in ~25% of cases.
- Spells are unlikely to occur more often than once a day and are not associated with an increased predisposition to epilepsy.

DIFFERENTIAL DIAGNOSIS

- Breath-holding spells
  - Because both forms of breath-holding spells potentially can terminate with seizure-like movements, differentiation between spells and epilepsy is important.
  - Occurrence of a precipitating factor (eg, minor injury, being frustrated) before spell onset indicates a breath-holding spell.
  - Patients with epilepsy display cyanosis during or after seizures, not before seizure onset.

DIAGNOSTIC PROCEDURES

- Electroencephalography
  - Electroencephalograms performed on patients who have breath-holding spells are typical when patients are not holding their breath.
  - Patients who have epilepsy often have abnormal encephalograms even during seizure-free periods.

TREATMENT APPROACH

Temper Tantrums

- Help parents cope with temper tantrums by
  - Providing anticipatory guidance
  - Sharing information on developmental psychology
  - Offering strategies to deal with tantrums

Breath-Holding Spells

- No effective medical therapy exists for breath-holding spells, although some toddlers who experience seizure-like activity along with spells are prescribed anticonvulsant therapy.

- The decision to use medication remains controversial among pediatric neurologists.

SPECIFIC TREATMENT

Temper Tantrums

- Encourage parents to describe how they think tantrums should be handled.
- Suggest books describing turbulent toddlerhood.
  - Brazelton's *Toddlers and Parents*
  - Ilg, Ames, and Baker's *Child Behavior*
  - Schmitt's *Your Child's Health*
- Ignore tantrums unless "they encroach on rights of others or potentially endanger" (Fraiberg S. *The Magic Years.* New York, NY: Charles Scribner's Sons; 1996).
- If safety is the issue
  - Institute environmental engineering (see Prevention section).
  - Restrict child to his bedroom for 2–3 minutes (use kitchen timer to remind parent and toddler of the time).
- Time-outs.
  - If child hits, bites, or throws in anger, for example, restrict child to room for 2–3 minutes.
    - Some behavioral psychologists suggest 1 minute of time-out for each year of age.
    - Others recommend that the time-out not be fixed; goal is to help the child develop self-regulation, so end the time-out when the tantrum subsides.
  - Briefly hug or praise, and then allow child to resume previous activity.
  - Parents may be reluctant to use bedroom restriction because they worry child will associate the bedroom with unpleasant experiences or will not feel remorseful if placed in a room full of toys.
    - Reassure parents that room restriction does not cause bedroom fears.
  - Goals of discipline are to teach rules and to help child understand which behaviors are acceptable.
  - Discipline does not need to be severe to be effective.
  - Once the tantrum is over, the slate is wiped clean and there is no holdover of judgment or anger, even if the child has acted out badly.
- "Time-ins"
  - Reward acceptable behavior.
  - When a toddler is playing quietly, pat the child on the shoulder, give a brief hug, or offer other nonverbal affection.
  - Some behavioral psychologists consider time-ins a more powerful method of encouraging acceptable behavior than time-outs.
- Tantrums with caregiver.
  - Temper tantrums are much less common in the presence of alternative child care providers than with parents.
  - Most experienced child care providers feel comfortable dealing with temper tantrums.
  - If the child care provider expresses concern to a parent about a child's temper tantrums, consider
    - Does the child care provider have adequate training?
    - Is this child care setting the most appropriate for the child (eg, adult to child ratio, philosophy of discipline, realistic expectations for behavior)?
    - Are temper tantrums much more severe or frequent than those of the child's peers?
  - Parents and the child care provider should formulate a plan that is followed consistently at home and at child care location.
  - If the parent and child care provider cannot agree on a plan, the child's primary care physician should be consulted.
- More specific guidelines for managing tantrums may be necessary in other individual situations.
- Encourage parents to vent feelings (to the physician) about tantrums and offer reassurance.

Breath-Holding Spells

- May be extremely difficult for parents.
- Spells that terminate with loss of consciousness or seizure-like movements are frightening.
- Convince parents that no harm will come to their child.
- Parents of a breath holder will frequently avoid enforcing limits for fear of precipitating an attack.
  - Such parents need repeated reassurance and encouragement to continue age-appropriate limits.

WHEN TO REFER

Temper Tantrums

- Parents who verbalize persistent frustration with tantrums or inability to cope with age-appropriate tantrums may need more comprehensive counseling.
- Parenting groups can help parents cope with negative behaviors.
  - Systematic Training for Effective Parenting
  - Parent Effectiveness Training

- If such services are not available or if more sophisticated professional counseling is obviously warranted, refer family to a counselor trained in psychiatry.
  - Discuss referral as soon as physician anticipates its necessity.
  - Stress involvement by both parents.
  - Maintain contact with the family about the problem after the referral has been made.
  - Ongoing contact may solidify the family's commitment to obtain and adhere with the counseling.

Breath-Holding Spells

- When to refer a breath-holding patient to a neurologist or a psychiatrically trained professional may not be an easy decision.
- If parents request further consultation, respect their wish even if you are confident that further evaluation is unnecessary.
- If parents agree with the physician that spells are of no consequence yet continue to withhold appropriate limit setting, refer parents to a mental health professional.
- The physician who is unsure of the diagnosis of breath-holding (especially if loss of consciousness or seizure-like activity occurs) should always refer the family to a pediatric neurologist.
- Referral must not end the physician-parent communication concerning the spells; ongoing dialogue may ensure adherence with the referral.

PROGNOSIS

- Children who display pallid breath-holding spells may, as adults, suffer from neurocardiogenic syncope, a form of vasovagal response to postural changes.

PREVENTION

Temper Tantrums

- Anticipatory guidance may forestall events that precipitate tantrums and prevent parental confusion in dealing with negative behaviors.
- Infancy.
  - Provide parents with anticipatory guidance on opportunities for positive interactions within daily routines and activities, such as feeding, pretend play, and reading aloud.
- 6-month visit.
  - Emphasize importance of parental time away from the infant.
  - Occasionally leaving child with responsible babysitters
    - Teaches child that adults can leave and then will return
    - Provides parents with mental health holidays from rigors of parenting
- 9- or 12-month visit.
  - Discuss environmental engineering to forestall potential adult-toddler power struggles over environmental dangers.
    - Providing home safety (eg, safety plugs in outlets, safety latches on drawers)
    - Removing valuables or breakables from reach
    - Ensuring a safe place for play (playpen or enclosed area)
- 15- or 18-month visit.
  - Offer the parent alternatives to negative interactions with the toddler.
    - Encouraging afternoon naps (for renewal of toddler and parental energy)
    - Praising cooperative toddler efforts
    - Offering limited decision-making ("Do you want to wear the green or blue shirt today?" versus "Which shirt do you want to wear today?")

DEFINITION

- *Tics* are recurring, nonrhythmic, sudden, rapid, stereotyped, involuntary movements or vocalizations.
- Tics may be classified as motor or vocal and as simple or complex.
  - The most common *simple motor tics* are
    - Eye blinking
    - Neck twisting
    - Shoulder shrugging
    - Grimacing
  - The most common *simple vocal tics* are
    - Coughing
    - Throat clearing
    - Sniffing
    - Grunting
  - *Complex motor tics* include more sustained, orchestrated, or seemingly purposeful gestures.
    - Touching, stomping on, or sniffing objects
    - Jumping
    - Sustained dystonic movements
    - Copropraxia (obscene gestures)
    - Echokinesis (automatic imitation of another person's movements)
  - *Complex vocal tics* include
    - Sudden changes in volume or prosody
    - Syllables, words, or stock phrases spoken out of context
    - Palilalia (repeating one's own words)
    - Echolalia (repeating the words of others)
    - Coprolalia (uttering obscenities)
  - Tic disorders are model neuropsychiatric conditions demonstrating the complex interplay of the following factors:
    - Genetic
    - Neurobiological
    - Environmental
    - Psychosocial

HISTORY

- Obtain history on potential prenatal and perinatal risk factors.
  - Maternal smoking
  - Vomiting and stress during pregnancy
  - Drugs
  - Fetal nutrition
  - Low birth weight
  - Exposure to androgens
- Careful clinical evaluation is needed to assess
  - Current phenomenology, history, and effect of the tics
  - Presence of other symptoms (eg, anxiety, impulsivity, inattention)
  - Adaptive difficulties in overall context of the child's social, family, and school life
- The possible role of any medications the child is receiving should be considered because removal or reduction may be the required treatment.
  - Stimulants
  - Sympathomimetics
  - Selective serotonin reuptake inhibitors (SSRIs) and other antidepressants
  - Neuroleptics
  - Androgenic steroids
  - Any drug that interferes with dopamine
- Tics wax and wane in intensity and frequency.
  - One tic disappears, and a new one takes its place.
- Stress or excitement often exacerbates tics.
- Children are generally unaware of their tics.
  - Premonitory urges are often reported in more severe cases or in older children.
- Tics are often transiently suppressible with effort.
  - This usually results in an increased urge to perform the tic.
  - Many patients describe their tics as neither fully voluntary nor involuntary.
  - Some consider the effort to suppress tics in social situations as burdensome as the tic.

PHYSICAL EXAMINATION

- The usual initial motor tics are blinking or facial grimacing, followed by rostral-caudal involvement.
- The most common initial vocal tics are
  - Sniffing
  - Coughing
  - Throat clearing
  - Symptoms are often initially mistaken for allergies, otolaryngological, or respiratory symptoms.
    - With tics, other characteristics of such disorders are absent.

DIFFERENTIAL DIAGNOSIS

- Assess tics, considering how to distinguish them from other neurologic disorders. Evaluate for
  - Stereotyped nature
  - Variability over time
  - Transient suppressibility
  - Accompanying premonitory urges
  - Lack of other neurologic symptoms

- Anxiety, stress, and excitement make existing tics worse and may precipitate them.
  - Children with anxiety disorders are overrepresented in clinical samples.
    - Little is known about the psychological status of most children in the general population who have tics because they are rarely seen in clinics.
    - Evidence exists for increased autonomic lability in individuals with Tourette syndrome (TS).
- Psychiatric disorders should be distinguished from psychological or stress factors because of severity.
  - Studies point to a relationship between tics and
    - Attention-deficit/hyperactivity disorder (ADHD)
    - Obsessive-compulsive disorder (OCD) with symptoms
      - Premonitory urges
      - Intrusive thoughts
      - Compulsive actions
- Many cases are genetic in origin.
- Drugs that may produce or exacerbate tics include
  - Amphetamines and other dopaminergic drugs
  - Cocaine and other stimulants
  - Sympathomimetics
  - Caffeine
  - SSRIs and other antidepressants
  - Anabolic steroids
  - Neuroleptics
- Distinguish tics from chorea.
  - Centripetal location
  - Repetitive form
  - Normal muscle tone
  - Lack of postural impersistence
- Distinguish true tics from stereotypies or self-stimulating behaviors, such as rocking, head banging, flapping, or spinning.
  - Tics are characterized by
    - Later onset
    - Lower complexity
    - Fluctuating intensity and locus
    - Intrusive, bothersome, disruptive, and involuntary nature
  - In contrast, stereotypies are bothersome to parents but not to the child.
    - The child finds them pleasurable and resists adult attempts to interrupt them.
  - Self-stimulating movements.
    - Mostly occur at times of boredom or excitement.
    - Rarely disrupt coordinated movements.
    - Persist without much change in form or location.
- The *Diagnostic and Statistical Manual of Mental Disorders,* 5th Edition, distinguishes 3 arbitrary subtypes of tic disorder.
  - Provisional
    - Present <1 year since first tic onset
  - Persistent (chronic)
    - Motor or vocal tics, but not both, persistent >1 year since first tic onset
  - TS
    - Multiple motor and at least one vocal tic, not necessarily concurrent, persisting ≥1 year from first tic onset
- Whether these 3 classifications reflect varying severity of the same disorder is unknown.
- Most recent research has been restricted to TS and suggests that these subtypes are probably related.

TREATMENT APPROACH

- Most tics in children are mild, are short lived, and do not require treatment.
- Once a tic has persisted for several months, treatment may be considered, if the tic is
  - Conspicuous
  - Disabling
  - Distressing to the child
- No treatment for tics can be said to be simple, entirely effective, or free of side effects.
- Pharmacotherapy.
  - Only physicians thoroughly familiar and experienced with the drugs indicated in children with tics should undertake pharmacotherapy.
  - The first consideration is deciding which symptom to target.
    - Tics
    - Comorbid conditions, such as OCD or ADHD
  - Because of frequent side effects (especially sedation), medication should be administered only when the tics are seriously disruptive, stigmatizing, or painful.
    - Start with a low dose.
    - Titrate the dose upward gradually.
    - Avoid sedation and cognitive blunting.
  - Set realistic goals in terms of tolerable levels.
    - Attempting to suppress tics completely often results in overmedication.
  - Discontinuing anti-tic medications should be done gradually.
    - Abrupt discontinuation may produce acute rebound or withdrawal-related exacerbations.

SPECIFIC TREATMENT

Behavioral Methods

- Although a variety of behavioral techniques have been tried for tic disorders, only comprehensive behavioral intervention for tics (CBIT) seems to have empirical support.
  - CBIT combines habit reversal and contingency management techniques.
  - Best carried out by a psychologist experienced with the technique in working with children.
- Anxiety-reducing and supportive interventions.
  - Relaxation training and biofeedback are not of proven value in treating tics.
  - Psychotherapy (specifically focused on stressful interpersonal difficulties), work with parents, and other means of reducing environmental stress may be helpful.
  - These procedures should be considered as ancillary.
  - Many children with tic disorders have difficulties at school, from comorbid conditions or peer stigmatization.
    - Close collaboration with school staff to ensure appropriate educational programming and accommodations is important.
- Acceptance interventions.
  - Explain to parents, teachers, and peers that tics are a physical disability and the child cannot help them.
  - Acceptance of the child and tics is the kindest, safest, and simplest way to deal with them.
    - Criticism is likely to make tics worse and prolong their course.
  - Peer problems can be a major difficulty.
    - Collaboration with school staff to reduce peer teasing and stigmatization is a major therapeutic task.
    - Support the child's strengths to bolster and protect his self-esteem.

Pharmacotherapy for Tics

- Various medications are effective in partially suppressing tics but are not curative.
- First choice: α-adrenergic agonists.
  - Clonidine.
  - Guanfacine.
  - Preferred because they are longer acting, less sedating, and more effective for attention problems.
  - Sustained-release forms of both are available.
  - It is usually preferable with young children to begin on smaller doses of the short-acting form, titrating slowly with small increments to avoid sedation.
  - Relatively benign; principal dose-related side effects are sedation and hypotension.
- Next line of agents: dopamine-blocking neuroleptics (antipsychotic drugs).
  - Appear to be effective because tics are executed through the basal ganglia.
  - There is apparent relative overactivity in the dopaminergic nigrostriatal systems that inhibits cholinergic basal ganglia systems.
  - Haloperidol, pimozide, or fluphenazine are preferred but have largely been replaced in clinical practice by newer, so-called atypical antipsychotics.
  - Even at relatively low doses, neuroleptics may produce
    - Acute dystonic reactions
    - Sedation
    - Cognitive blunting
    - Medication-induced separation anxiety
    - Parkinsonism
    - Akathisia (restless legs)
  - If moderate doses are not effective, higher doses, with increased side effects, are not likely to be.
  - Higher doses make it difficult to wean the patient without rebound exacerbation.
- In many patients, typical antipsychotics are now being replaced by atypical antipsychotics, such as
  - Risperidone, olanzapine, and ziprasidone.
  - Atypical neuroleptics have the same adverse effects as typical neuroleptics.
    - Acute dystonic or extrapyramidal reactions, sedation, or dysphoria
    - Hyperphagia and weight gain, with potentially serious metabolic consequences (risperidone and olanzapine)
- When neither α-adrenergic agents nor neuroleptics are effective, a variety of second-line drugs or augmentation strategies may be tried with caution.
  - Clonazepam should only be used in unusual instances.
    - Side effects: cognitive blunting, sedation, irritability, disinhibition
    - Can lead to dependence and withdrawal symptoms

Pharmacotherapy for Comorbid Conditions

- These include ADHD, OCD, anxiety, or depression.
- Stimulants may increase tics or precipitate new tics.
- ADHD is often more disabling than tics.
  - A cautious trial of a stimulant may be necessary, beginning with very low doses and increasing gradually.
  - Alternatives to the stimulants are
    - — α-Adrenergic agents (clonidine or guanfacine)
    - — Atomoxetine (may also increase tics)
  - Second-line drugs are older tricyclic antidepressants.
    - — Initiate electrocardiographic monitoring.
  - Most children with tics and ADHD can tolerate methylphenidate.
    - — The combination of methylphenidate and clonidine is better than either agent alone.
- SSRIs are effective in children with OCD and tics.
  - Evidence suggests that monotherapy with SSRIs is less effective in the presence of tics.
  - Augmentation with a low dose of a neuroleptic often boosts response.
  - In rare cases, SSRIs can exacerbate or even precipitate tics, akathisia, or other movement abnormalities or can increase suicidal thinking.

WHEN TO REFER

- Referral is likely to be influenced by associated problems, and emphasis of treatment may, thus, focus less on tics than in mapping other areas of dysfunction.
- Criteria for referring children who have tics to a mental health specialist include
  - Tics associated with additional evidence of a psychiatric disorder, such as ADHD, generalized anxiety, or OCD
  - Chronic or recurrent tics that seem to have a clear relationship to stress, particularly if there is reason to believe that psychosocial interventions may be helpful
  - Chronic, disabling, or discomforting tics for which differential diagnosis or treatment is needed
  - Primary physician with little knowledge about tics who wants an expert opinion
  - When psychoactive drugs, such as antipsychotics (neuroleptics) or clonidine, may be indicated
    - — Psychiatrists routinely use these medications and are well informed about risks, side effects, dose levels, and newer drugs.
- Referral may be only for consultation, not necessarily for continued management.
- The preferred mental health specialist is a well-trained child or adolescent psychiatrist with
  - Broad biopsychosocial perspective
  - Knowledge of neuropsychiatry and pharmacotherapy
  - Capacity to work closely with behavioral psychologists
  - Awareness of the possibilities of rare neurologically induced tics
    - — To order appropriate neuroimaging and neurologic consultations
- Referral should be made to a child psychologist experienced in behavioral treatment when
  - The tic is disabling and no further diagnostic workup is required.
  - Pharmacotherapy is not an option or is already in place, but further relief is necessary.
  - The child is having difficulties at school that are not simply caused by teasing or distraction of tics.
- Many children with tic disorders benefit from close collaboration with their school.
  - Making the teacher aware of the tics
  - Providing accommodations such as the ability to step out of class briefly when tics are intrusive

WHEN TO ADMIT

- Never for tics alone
- Occasionally for
  - Complex assessments to initiate treatments
  - Tapering a child from high doses of multiple medications

COMPLICATIONS

- Children with tics and, especially, TS can experience related problems of self-image when adult criticism and peer rejection result.
- Persistent tics are associated with an increased risk of comorbid ADHD.
  - Predates the tics or any accompanying OCD.
  - Children with combined ADHD and tics have the greatest social and academic difficulties.
  - ADHD severity is a better predictor of poor adjustment than tic severity.
  - Chronic tics are often associated with learning impairment independent of ADHD.
- Individuals with TS are also at risk for
  - Other anxiety disorders.
  - Depression.

- Fine-motor difficulties.
- Uneven cognitive profile.
  - Performance IQ scores are lower than verbal IQ scores.
- ADHD is common and is seen in 50% of patients with TS.
- OCD is found in up to 50% of patients with TS.
  - Most common compulsions and obsessions are around
    - Symmetry
    - Evening up
    - Sex
    - Aggression
- OCD may develop during adolescence or late in TS.
- OCD can be a persistent source of distress despite the improvement in tic severity with age.

■ Occasionally, severe complex motor tics result in injury or self-mutilation.

PROGNOSIS

■ Most tics last only a few weeks.
- Tics may flit from one muscle group to another.
- Tics change their form at irregular intervals.

■ Even the chronic tics of TS are likely to disappear in later adolescence.
- Although most tics improve by late adolescence, OCD or ADHD symptoms may persist.

■ Prevalence of tics drops sharply >13 years.
- Tics that persist into later adolescence are more likely to become chronic.

■ Tic severity in adulthood is inversely proportional to
- Caudate volume in childhood
- Childhood performance on a dominant hand fine-motor skill test

Tonsillectomy and Adenoidectomy

BACKGROUND

- *Tonsillectomy* is surgical removal of the tonsils.
- *Adenoidectomy* is surgical removal of the adenoids.
- Tonsillectomy and adenoidectomy (T/A) are 2 of the most common surgical procedures performed on children worldwide.
- Obstructive sleep apnea syndrome (OSAS): disorder of breathing during sleep.
  - Characterized by prolonged partial airway obstruction or intermittent complete obstruction that disrupts normal ventilation during sleep and normal sleep patterns
- Sleep-disordered breathing (SDB): abnormalities of respiratory pattern or adequacy of ventilation during sleep, which includes snoring, mouth breathing, and pauses in breathing.
  - A spectrum of disorders from snoring to OSAS

GOALS

OSAS or SDB

- Nonobese children with SDB who undergo T/A can expect resolution of symptoms 70%–80% of the time.
- Patients with the following conditions are less likely to have complete resolution of sleep abnormalities after T/A and may warrant postoperative polysomnography (PSG):
  - Obesity (resolution of symptoms in only 10%–25% of patients)
  - Neuromuscular weakness
  - Craniofacial anomalies
  - Severe preoperative OSAS
  - Family history of sleep apnea
  - African American ethnicity
- Childhood Adenotonsillectomy Trial.
  - No difference in executive function or attention for those undergoing T/A.
    - Measured by Developmental Neuropsychological Assessment 6–7 months postoperatively
  - Improvement in the T/A group in
    - Conners rating scales (teacher and parent)
    - Epworth Sleepiness Scale
    - 2 quality-of-life measures
  - On PSG, significantly greater improvement in
    - Apnea-hypopnea index (AHI) score
    - Oxygen desaturation index
    - Hypercapnia
    - Arousal index
  - Obese children with T/A improved in many measured parameters.

Recurrent Tonsillitis

- Reduction of throat infections and elimination of tonsillitis
  - Most experts recommend surgery only for patients with recurrent pharyngitis who meet Pittsburgh criteria, because of costs and complications of surgery.
    - After consultation with caregivers about risk of complications versus benefits, watchful waiting is reasonable even for these patients.
    - American Academy of Otolaryngology–Head and Neck Surgery (AAO) guidelines recommend assessing for modifying factors in children with recurrent throat infection who do not meet Pittsburgh criteria.[1]
      - Multiple antibiotic allergies making treatment of recurrence difficult
      - Recurrent pharyngitis associated with peritonsillar abscess
      - Periodic fever, aphthous stomatitis, pharyngitis, and adenitis
  - In one study, children who had tonsillectomy consistently had fewer throat infections, particularly in episodes rated moderate or severe.
    - Despite better outcomes in the surgical group, rates of infection in the control group in subsequent years were relatively low, favoring observation over intervention.
    - A complication rate of 14% occurred in the surgical group; all were self-limited and readily managed.
  - More recent research analyzed T/A for patients with less severe criteria.
    - Differences between the surgical group and controls were statistically but not clinically significant.
    - Moderate inclusion criteria did not justify the risks of surgery, including morbidity (7.9% complication rate) and cost.
  - In another study in which a wait-and-see approach was proposed for patients who do not meet Pittsburgh criteria
    - 4% complication rate.
    - 1% required surgery for hemorrhage.
    - 2.6% had severe nausea or dehydration.
    - Did not justify minimal reductions in the frequency of tonsillitis.
  - A Cochrane systematic review revealed minimal benefit.

- 2 other systematic reviews showed just modest improvement in those who had T/A; control group in both also showed significant improvement in tonsillitis episodes.

Adenoidectomy

- Adenoidectomy without tonsillectomy considered for
  - Chronic otitis media with effusion if pressure-equalization tubes need reinsertion.
    - Especially in children >4 years
  - Significant nasal obstruction.
  - Recurrent sinusitis.
  - Chronic adenoiditis.
  - Adenoidectomy alone has not been studied as well as T/A.

GENERAL APPROACH

OSAS

- American Academy of Pediatrics (AAP) and AAO guidelines agree that T/A should be performed in a child with symptoms of SDB with significant OSAS on PSG and adenotonsillar hypertrophy, barring contraindications.
- Most references define abnormal PSG to be an AHI >1 or pulse oximetry <92%.
  - In practice, most otolaryngologists consider an AHI score of 5 to indicate OSAS severe enough for surgery.
  - T/A may be indicated for symptomatic patients with lower AHI because evidence has not yet defined specific parameters.
  - PSG results do not always correlate with clinical symptoms preoperatively or postoperatively.
- Tonsillar enlargement is considered a requirement for T/A; however, it is not always correlated with PSG results.
  - Significant hypertrophy is diagnosed when tonsils fill >50% of transverse tonsillar space.
  - In abnormal PSG without hypertrophy on visual examination of the pharynx, lateral neck films may show tonsillar obstruction below the oropharynx or adenoidal obstruction in the nasopharynx.
- PSG.
  - Gold standard for assessing children for OSAS.
  - In clinical practice, <10% of children and adolescents who undergo T/A have preoperative PSG.
    - Patients without risk factors listed in the AAO guidelines who have significant symptoms of SDB and tonsillar hypertrophy will likely undergo T/A without PSG if referred directly to an otolaryngologist.
      - Direct referral in this situation is supported by AAP guidelines.
  - ~10% of children have nighttime snoring, but only one-third of these have OSAS on PSG.
  - AAP guidelines: snoring history plus any of the following criteria:
    - Positive history for
      - Symptoms of SDB
      - Frequent snoring (>3 nights/wk)
      - Labored breathing during sleep
      - Gasps/snorting noises/observed episodes of apnea during sleep
      - Sleep enuresis
      - Sleeping in a sitting position or with neck hyperextended
      - Cyanosis
      - Headaches on awakening
      - Daytime sleepiness
      - Attention-deficit/hyperactivity disorder symptoms
      - Learning problems
    - Physical examination reveals
      - Tonsillar hypertrophy
      - Underweight or overweight
      - Adenoidal facies
      - Micrognathia/retrognathia
      - High arched palate
      - Failure to thrive
      - Hypertension
  - AAO guidelines.
    - Obesity
    - Down syndrome
    - Craniofacial abnormalities
    - Neuromuscular disorders
    - Sickle cell disease or mucopolysaccharidoses
    - Uncertainty between physical findings and history
  - PSG also used for postoperative monitoring.

Recurrent Tonsillitis

- AAO guideline recommends watchful waiting for children who do not meet Pittsburgh criteria.[2]
  - Frequency criteria.
    - 7 episodes in the past year
    - 5 episodes per year for the past 2 years
    - 3 episodes per year for the past 3 years
  - Sore throat plus one of the following clinical features:
    - Temperature >38.3°C (101°F) *or*
    - Cervical lymphadenopathy >2 cm *or*
    - Tonsillar exudate *or*

- — Positive test result for group A β-hemolytic streptococci
- *Plus* antibiotics for proven or possible streptococcal infection.
- If not documented, physician should observe patient closely to determine if described clinical pattern is continuing prospectively.

Other Indications

- Tonsillectomy in cases of suspected malignancy where there is asymmetric tonsillar hypertrophy in the setting of
  - Lymphadenopathy >3 cm
  - Splenomegaly
  - Fever
  - Sweats
- Indications for T/A that lack evidence; theoretical benefits for these conditions do not justify risk of surgery.
  - Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections
  - Chronic tonsillitis
  - Muffled speech
  - Halitosis
  - Malocclusion of teeth
  - Group A β-hemolytic carrier state

Contraindications

- Relative contraindications for T/A include
  - Uncontrolled bleeding disorders
  - Medical conditions causing patient to be unstable for anesthesia
  - Patients with submucosal cleft palate at risk for velopharyngeal insufficiency after T/A
    - — Evaluate for presence of bifid uvula or notched hard palate as preoperative clues to this diagnosis.

SPECIFIC INTERVENTIONS

Medical Management of OSAS

- Topical intranasal corticosteroids for mild OSAS or when T/A is contraindicated
- Recent demonstration of benefit from montelukast for nonobese children with mild OSAS (AHI <10)
  - AHI decreased by >50% in 65.2% of patients after 12 weeks of medication.
- Adjunctive treatments for children who do not respond to T/A
  - Continuous positive airway pressure
  - Weight loss
  - Montelukast
  - Possible treatment with nasal steroids

Perioperative Medication

- Steroids
  - AAO guidelines recommend one intraoperative dose of intravenous dexamethasone to children undergoing T/A.
    - — Dose 0.0625–1 mg/kg; total dose range 8–25 mg
    - — Demonstrated to reduce postoperative nausea and vomiting (relative risk 0.54; 0.42–0.69) with 4 being the number needed to treat
    - — Less postoperative throat pain and earlier return of oral intake
    - — No significant negative consequences
- Antibiotics
  - AAO guidelines strongly recommend against perioperative antibiotics.
    - — Cochrane review showed no significant benefit.
- Analgesia
  - Pain generally lasts a week or more and can lead to poor oral intake and dehydration.
  - Important to maintain adequate hydration.
  - No demonstrated benefit of around-the-clock over as-needed analgesia.
  - Use of narcotics, especially codeine, under increased scrutiny following reports of death after T/A.
    - — Best practice is to avoid codeine analgesia.
    - — Current practice is to use non-codeine opiates when acetaminophen or ibuprofen are not controlling pain.
    - — More research is needed to determine risk in non-codeine opiates (eg, oxycodone, hydrocodone).
  - Acetaminophen
    - — 15 mg/kg/dose (maximum dose of 75 mg/kg/d, in ≤5 divided doses/d with 4,000 mg/d)
  - Ibuprofen
    - — 5–10 mg/kg/dose up to 4 times/d (maximum dose of 40 mg/kg/d); administer with food if gastrointestinal upset occurs
  - Opioids
    - — Note: For opioid analgesia, consider reducing dose by 33%–50% for patients at risk for or documented to have OSAS.
    - — Oxycodone.
      - Patient weight <50 kg, >6 months: oral: initial dose: 0.1–0.2 mg/kg/dose every 4–6 hours as needed; for severe pain, some experts have recommended an initial dose of 0.2 mg/kg/dose; usual maximum dose range: 5–10 mg.

- Patient weight ≥50 kg: oral: initial dose: 5–10 mg every 4–6 hours as needed; for severe pain, an initial dose of 10 mg may be used; usual maximum dose: 20 mg/dose.

— Hydrocodone and acetaminophen (Norco).
- Patient weight <50 kg: oral: usual initial dose: hydrocodone 0.1–0.2 mg/kg/dose every 4–6 hours.
- Patient weight ≥50 kg: oral: usual initial dose: hydrocodone 5–10 mg every 4–6 hours.
- Note: Opioid-naive patients—limited data available in infants and children <2 years; use caution. Also, the maximum daily dose of acetaminophen should be limited to ≤75 mg/kg/d in ≤5 divided doses and should not exceed 4,000 mg/d.

T/A

- Classic technique
  - Cold dissection of tonsils with a scalpel, surgical scissors, guillotine, or snare
    - Separates capsule from superior pharyngeal constrictor muscle and gaining hemostasis with suture ligature
  - Adenoidectomy: curettage
  - Still considered safe but can be associated with considerable blood loss
- Current preferred technique
  - Monopolar electrocautery to vaporize adenoid tissue and dissect tonsils from the fossae
    - Little or no blood loss.
    - Relatively inexpensive; widely available.
    - May increase risk of secondary hemorrhage and postoperative pain because of thermal injury to underlying constrictor muscle.
- Surgical lasers
  - Used in T/A for the past 2 decades.
  - Less superior pharyngeal constrictor muscle injury.
  - Better hemostasis.
  - Less pain than with the more popular electrocautery technique.
  - Electrocautery may be required as an adjunct to achieve hemostasis.
- Other techniques for tonsil removal with less potential for thermal injury to surrounding tissue include
  - Harmonic scalpel
  - Coblation device
  - Peak plasma blade
  - Intracapsular technique
    - Removal of only 90%–95% of tonsil, leaving tonsillar capsule to cover superior constrictor muscle
    - Alternative procedure for younger patients with obstructed breathing
    - May not be appropriate for patients with recurrent infections
- Inpatient versus outpatient setting
  - Decision rests on presence of risk factors; no consensus as to what PSG indications require inpatient monitoring.
  - Potential indications for inpatient T/A include
    - <3 years
    - Score of ≥5 on the scoring system for perioperative risk, found in the American Society of Anesthesiologists (ASA) "Practice Guidelines for the Perioperative Management of Patients With Obstructive Sleep Apnea"
    - Severe OSAS on PSG (AHI ≥24 in the AAP guidelines vs >10 in the ASA, AAO guidelines); significant hypercapnia (partial pressure of carbon dioxide ≥60 mm Hg)
    - Lowest oxygen saturation <80% (on preoperative PSG or during observation in the recovery room postoperatively)
    - Cardiac complications of OSAS
    - Failure to thrive
    - Obesity
    - Craniofacial anomalies
    - Neuromuscular disorders
    - Current or recent respiratory infection
    - Significant asthma
    - African American race (4-fold increased risk of OSAS)
    - Down syndrome
    - Mucopolysaccharidosis and other serious metabolic disorders
    - Sickle cell disease
    - Central apnea

Complications

- Life-threatening situations are rare and generally result from catastrophic hemorrhagic and respiratory complications.
- Mortality rates after tonsillectomy are difficult to estimate because death is such a rare outcome.
- Most common complications (**Table 1**) include
  - Bleeding
    - Minor, postoperative bleeding in 1%–2% of all cases in the United States.

Table 1. Post–Tonsillectomy/Adenoidectomy Complications

Complication	Onset	Presentation	Treatment
Immediate hemorrhage	0–24 h	Oral bleeding	Exploration and ligation of blood vessel
		Hemoptysis	
		Hematemesis	
Delayed hemorrhage	5–14 d	Oral bleeding	Ice pack to neck and iced liquids
		Hemoptysis	Elevation of head and neck
		Hematemesis	Silver nitrate cautery Blood vessel ligation Coagulopathy workup
Immediate airway compromise	Extubation–2 h	Cyanosis, stridor	Rule out upper airway obstruction/aspiration. Rule out laryngospasm. Rule out pulmonary edema.
Delayed airway compromise	2–24 h	Shortness of breath	Intravenous or oral steroid
		Stridor	Nasopharyngeal airway
Dehydration	1–6 d	Lethargy	Intravenous rehydration
		Tachycardia	Pain control, hydration
		Anuria/oliguria	Parent education

  - Postoperative hemorrhage within 24 hours of T/A is generally thought to be related to surgical technique.
  - Hemorrhage ~1–2 weeks after surgery is without identifiable cause.
- Aspiration
- Cardiopulmonary failure
- Electrolyte imbalance
- Anesthetic complications
- Airway compromise/apnea
  - Postoperative airway obstruction mainly in children <3 years caused by edema of palate, tongue, or lateral pharynx

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DEFINITION

- The word *torticollis* originates from 2 Latin words: *tortus,* meaning twisted, and *collum,* meaning neck.
- The classic clinical picture of torticollis is of the head tilted to one side and rotated in such a way that the chin and face point to the contralateral side.
- Torticollis can be broadly classified as 1 of 2 types.
  - Congenital
  - Acquired
- Facial asymmetry is often observed in congenital torticollis but not in acquired torticollis.
  - This finding can be useful in clinically distinguishing between the 2 forms.

HISTORY

- Obtain a thorough and detailed history.
- Particular attention should be given to
  - Duration of symptoms
  - Previous trauma
  - Presence of fever
  - Other systemic manifestations, including other musculoskeletal system symptoms
- In younger patients, the birth history is essential.

PHYSICAL EXAMINATION

- Physical examination should not be limited to the head and neck.
  - Include all organ systems.
  - Perform thorough examination of the musculoskeletal system.
    - Muscle tone
    - Muscle strength
    - Hip positions
    - Alignment of the lower extremities and feet
    - All vertebrae, with attention to presence of sacral dimples
    - Peripheral joints to assess for evidence of arthritis via joint swelling or limitations of movement in association with pain, warmth or redness
  - Perform a thorough neurologic examination.
    - Cranial nerves
    - Vision
    - Sensation
    - Reflexes
    - Fine and gross motor skills
    - Cerebellar testing
- Such findings as craniofacial asymmetry suggest a congenital torticollis of long duration.
  - Plagiocephaly can be the presenting sign of mild torticollis.
- Webs or cysts in the neck should raise the suspicion of pterygium colli or remnant cysts.
- Patients with acquired torticollis as a result of trauma often have a tender sternocleidomastoid muscle (SCM).
- Point tenderness over the cervical spine may suggest an underlying fracture or subluxation.
  - Cervical vertebral osteomyelitis should be suspected in patients who have point tenderness in association with unexplained fever.

DIFFERENTIAL DIAGNOSIS

Congenital

- Muscular torticollis
- Postural torticollis
- Cervical spine anomalies
- Hemivertebra
- Atlantooccipital fusion
- Klippel-Feil syndrome
- Sprengel deformity
- Pterygium colli (webbed neck)
- Sternocleidomastoid cysts
- Cystic hygroma
- Bronchial cleft cyst
- Unilateral absence of sternocleidomastoid
- Occipital condylar dysplasia

Acquired

- Muscular
  - Cervical muscle injury
    - Traumatic
    - Awkward positioning during sleep
- Vertebral
  - Atlantoaxial subluxation
    - Laxity of the transverse cervical ligaments results in atlantoaxial instability in up to 15% of patients with Down syndrome.
  - C2-3 subluxation
  - Rotary subluxation
  - Cervical fractures
  - Cervical vertebral osteomyelitis
  - Juvenile idiopathic arthritis (JIA)
    - Torticollis may, rarely, be the presenting finding in systemic onset or polyarticular JIA.
    - Inflammatory reactions around the spine produce hyperemia and edema, which lead to laxity of the supporting ligaments and a predisposition to spontaneous subluxations and torticollis.
  - Acute cervical disk calcification caused by trauma or respiratory infection

- Infectious
  - Infection of the head and neck (Grisel syndrome)
  - Upper respiratory infection
  - Retropharyngeal abscess
  - Cervical lymphadenitis
  - Cervical vertebral osteomyelitis
  - Dental infection
- Neurologic
  - Ocular torticollis with
    - Strabismus
    - Nystagmus
    - Refractive errors
    - Paralysis of extraocular muscles
  - Spasmus nutans (nystagmus, head nodding, and torticollis)
    - No known cause.
    - Signs and symptoms usually develop within the first 2 years of life.
    - May persist for months to years, but the course is often benign and self-limited.
    - But if accompanied by ataxia, suspect a cerebellar tumor.
  - Dystonic torticollis
    - May follow the administration of phenothiazines, carbamazepine, or phenytoin.
    - Presence of other extrapyramidal signs can confirm a dystonic reaction.
  - Syringomyelia
  - Epidural hematoma
  - Labyrinthine torticollis
  - Brachial plexus palsy
  - Arnold-Chiari malformation
  - Accessory nerve palsy
  - Acute disseminated encephalomyelitis
  - Wilson disease
- Neoplastic
  - Cervical cord tumor
  - Posterior fossa tumor
  - Soft tissue tumor
  - Langerhans cell histiocytosis (histiocytosis X)
  - Infantile desmoid fibromatosis
- Other
  - Benign paroxysmal torticollis
  - Psychogenic torticollis
  - Sandifer syndrome
    - An abnormal posturing that includes torticollis and opisthotonos
    - Believed to be a protective mechanism adopted by some patients with gastroesophageal reflux, esophagitis, or hiatal hernia
  - Dermatogenic torticollis
    - A painful, stiff neck resulting from extensive local skin lesions
  - Spurious torticollis
    - Stiffness of the neck from dental malformations or caries

LABORATORY EVALUATION

- Helpful adjuncts to diagnose torticollis caused by infection or inflammation
  - Peripheral leukocytosis
  - Increased sedimentation rate

IMAGING

- Imaging of the cervical spine should be obtained
  - In all neonates with torticollis
  - In older children with findings that suggest vertebral involvement
  - In older children with persistent torticollis
- Ultrasonography is the imaging modality of choice for initial evaluation.
- Patients with neurologic deficits should undergo prompt computed tomography or magnetic resonance imaging of the head and neck.
- Several congenital cervical spine anomalies can occur in conjunction with torticollis.
  - Most of these anomalies can be diagnosed by radiographic studies of the cervical spine.
    - Pterygium colli, a congenital web of the skin of the neck extending from the acromial process to the mastoid, can be restrictive and result in torticollis.
    - Congenital remnant cysts within the body of the SCM are a less common cause of torticollis.
    - Unilateral absence of one SCM results in unopposed action of the other muscle and produces a contralateral torticollis.

TREATMENT APPROACH

- Congenital muscular torticollis responds well to prompt conservative treatment during the first year of life.
- The treatment of acquired torticollis arising from other specific diseases should be directed at the cause.
- Any child with severe neck pain or tenderness over the vertebra requires immediate cervical immobilization until radiography can be performed to exclude the possibility of vertebral fracture or subluxation.

SPECIFIC TREATMENT

Congenital Torticollis

- Medical management includes passive and active stretching of the neck.
  - Gentle (passive) stretching can be performed daily by parents or a physical therapist.
  - Active stretching.
    - Manipulate the infant's environment in such a way that objects of interest are located on the side of the room opposite to the torticollis to induce the infant to turn his neck in the desired direction.
- Surgical correction is essential if
  - Deformity persists beyond the first year of life.
  - Range of motion is restricted >30%.
  - Residual craniofacial deformity exists.
- Craniofacial asymmetry is best reversed early, when the child's growth potential is at its maximum.
- The surgical procedure that has the best results involves
  - Bipolar tenotomy of the affected SCM
  - Followed by casting or bracing to maintain the corrected posture

Acquired Torticollis

- Acquired muscular or ligamentous torticollis should be managed with
  - Local heat
  - Massage
  - Analgesics
  - Muscle relaxants
  - Soft cervical collar
- Symptoms usually resolve in 7–10 days.
- Patients with acquired muscular or ligamentous torticollis experience only mild discomfort.
- For drug-induced dystonic reaction
  - Discontinue the offending drug.
  - Administer intravenous diphenhydramine.

WHEN TO REFER

- Presence of craniofacial asymmetry
- Radiographic evidence of cervical spine abnormality
- >30% restriction in range of motion
- Persistence beyond the first year of life

WHEN TO ADMIT

- Presence of neurologic deficits
- Severe neck pain
- Point tenderness over the vertebrae

FOLLOW-UP

- Congenital torticollis should be followed carefully for development or worsening of craniofacial deformities.

COMPLICATIONS

- If not treated appropriately, patients with congenital torticollis may develop craniofacial deformities or worsen existing craniofacial deformities.
  - The twisted position of the neck can lead to positional plagiocephaly.
  - Skull flattening on the contralateral side may result from sleeping supine.

Turner Syndrome and Noonan Syndrome 1160

DEFINITION

Turner Syndrome (TS)

- A phenotype of girls genetically characterized by an abnormal or missing X chromosome
- Features include
  - Short stature
  - Gonadal failure
  - Varying degrees of skeletal, cardiovascular, renal, endocrine, lymphatic, and neurodevelopmental abnormalities

Noonan Syndrome (NS)

- Genetic mutation with a different etiology but with a similar phenotype to TS
  - Short stature
  - Neck webbing
  - Gonadal failure (in males)
  - Distinct facial features
  - Frequent cardiac, endocrine, skeletal, neurologic, and hematologic abnormalities

SIGNS AND SYMPTOMS

TS

- Presentation can be heterogeneous because of haploinsufficiency of genes encoded on the X chromosome.
- Cardiovascular defects are common.
  - Typically involve right-sided malformations.
  - Coarctation of the aorta.
  - Bicuspid aortic valve.
  - Aortic root dilation/dissection.
  - Hypertension.
  - Lymphatic accumulation can be associated with fetal hydrops, pleural effusions, lymphangiectasis, and anomalous lymphatic vessels.
- Craniofacial.
  - Epicanthal folds
  - Excess nuchal skin
  - Webbed neck
  - Low posterior hairline
- Dermatologic.
  - Pigmented nevi; however, risk for melanoma is not increased over the general population.
  - Generalized lymphedema with excessive nuchal skin, easy bruising, and hyperpigmentation.
  - Increased likelihood of keloid scarring.
- Endocrine system and growth.
  - Hypothyroidism.
  - Infants often have some degree of intrauterine growth restriction and postnatal growth lags behind that of other children.
  - Feeding difficulties can negatively affect nutrition and weight gain.
  - Most girls with TS have delayed childhood growth and lack of a pubertal growth spurt.
  - Short stature.
    - — *SHOX* gene deficiency resulting from the loss of all or part of the X chromosome
- Genitourinary.
  - Gonadal dysgenesis—leads to delayed/absent puberty
  - Streak ovaries (most infertile)
  - Renal malformations (horseshoe kidneys most common)
- Musculoskeletal.
  - Lymphedema of hands and feet at birth
  - Deep-set hyperconvex nails
  - Short fourth metacarpals
  - Cubitus valgus
  - Broad chest with wide-spaced nipples
  - Scoliosis
- Neurodevelopmental.
  - Learning difficulties (typically normal intelligence)
  - Lower scores on assessments of nonverbal learning, reduced speed in mental processing, or deficits in executive function
- Ophthalmologic.
  - Strabismus
- Otolaryngological.
  - Hearing loss
- Orthodontics.
  - Narrow maxilla and small mandible commonly lead to
    - — Dental malocclusion
    - — Articulation defects
    - — Micrognathia
    - — Crowded teeth
  - Orthodontic evaluation is begun by 7 years of age.

NS

- Cardiovascular
  - Pulmonic stenosis
  - Hypertrophic cardiomyopathy
  - Lymphatic abnormalities
- Craniofacial
  - Low-set or posteriorly rotated ears
  - Fleshy helices
  - Hypertelorism
  - Downward-slanting palpebral fissures
  - Epicanthal folds
  - Ptosis

- Thick eyelids
- Broad, webbed neck

- Endocrine and growth
  - Growth hormone (GH)-secretory dynamics reflect the existing genetic heterogenicity, and both GH sufficiency and GH deficiency have been reported.
  - Insulin-like growth factor 1 is often lower in *PTPN11* mutation-positive NS patients, which may point to some degree of GH resistance when associated with normal GH secretion.
  - Birth length is typically preserved.
  - Birth weight is often low.
  - Height standard deviation (SD) scores and growth kinetics can vary depending on the exact genetic mutation encountered in the Ras/MAPK pathway.
    - Mean adult height only reaches lower limits of typical late in the second decade of life.
    - Delayed puberty causes delay in growth spurts for boys and girls.
- Hematologic
  - Higher than normal risk for bleeding disorders
    - Coagulation-factor anomalies
      - Thrombocytopenia
      - Platelet dysfunction
      - Deficiencies in factors VIII, XI, or XII
- Dental and orthodontic
  - Dental malocclusion
  - Articulation defects
  - Micrognathia
  - Crowded teeth
- Lymphedema, excessive nuchal skin, easy bruising, and hyperpigmentation
- Musculoskeletal
  - Superior pectus carinatum with inferior pectus excavatum
  - Low-set nipples
- Neurodevelopmental
  - Developmental delay.
  - Mild intellectual disability (may be present in one-third of cases).
  - The neurologic and behavioral aspects of NS are less well understood and quite variable.
  - Learning disabilities, peripheral neuropathy, and seizures are all increased in NS patients compared with nonsyndromic children.
  - Although brain structural malformations are relatively uncommon, Arnold-Chiari type I malformations and hydrocephalus are known to occur at low frequencies.
  - Generalized motor delay is present in most.
  - Body image problems and poor self-esteem, depression, and feelings of social inadequacy have all been noted in adolescents and adults with NS.
- Ophthalmologic
  - Strabismus
- Otolaryngological
  - Hearing loss
- Renal and genitourinary
  - Renal anomalies have been reported in 10%–11% of patients with NS.
  - Solitary kidney.
  - Renal pelvic dilation.
  - Duplicated collecting system.
  - Often clinically insignificant.
  - Fertility does not seem to be affected in females with NS.

DIFFERENTIAL DIAGNOSIS

- Clinical features of TS and NS overlap somewhat, but each is a distinct diagnosis with a specific genetic etiology (**Table 1**).

TS

- Any disorder causing growth failure or short stature in females.
  - Hypothyroidism
  - GH deficiency
  - Skeletal dysplasia
  - Chronic illness
  - Normal short stature variants
- Delayed puberty and amenorrhea must be distinguished from other causes of ovarian failure (eg, long-term survivors of childhood neoplasia, autoimmune ovarian disease).

NS

- Syndromes with overlapping phenotypes.
  - Cardio-facio-cutaneous syndrome
  - Costello syndrome
  - Neurofibromatosis 1
  - LEOPARD syndrome (multiple **l**entigines, **e**lectrocardiogram conduction abnormalities, **o**cular hypertelorism, **p**ulmonic stenosis, **a**bnormal genitalia, **r**etardation of growth, and **d**eafness)
- Syndromes with distinct facial dysmorphology, cardiac defects, and short stature (Williams and Aarskog syndromes) may be difficult to differentiate from NS.

Table 1. Phenotypic Overlap of Turner and Noonan Syndromes

Similarities	Differences
Short stature (most)	Genetic etiology TS: loss of X chromosome material NS: mutation in *PTPN11* (or other genes)
Pubertal delay (most TS, some NS)	Cardiac anomalies TS: left-sided NS: right-sided
Eyelid ptosis	Neurobehavioral TS: nonverbal learning deficits NS: global developmental delay, seizures
Increased inter-nipple distance	Gonadal dysgenesis in most girls with TS
Webbed neck	Normal fertility in girls with NS
Kidney malformations	
Chronic otitis media	

Abbreviations: NS, Noonan syndrome; TS, Turner syndrome.

DIAGNOSTIC APPROACH

TS

- Often diagnosed late (late childhood and beyond).
- Increasingly diagnosed prenatally through amniocentesis or chorionic villus sampling.
- If a karyotype was obtained in utero, it should be repeated following birth.

NS

- Noonan Spectrum Panel performed by next-generation gene sequencing allows for a comprehensive analysis of potentially pathologic variants that may offer definitive diagnosis.
  - Frequency of gene mutations among patients with NS is only ~60%.
  - Lack of a detectable genetic mutation does not rule out a diagnosis when there is a strong clinical suspicion.
- Prenatal diagnosis.
  - Amniocentesis or chorionic villus sampling

LABORATORY FINDINGS

TS

- Karyotyping with a minimum of 30 cells in metaphase will identify at least 10% mosaicism with 95% confidence.
- Test for Y chromosome material by fluorescent in situ hybridization in any patient with chromosome material of unknown origin.
- Consider cytogenetic analysis for all females with unexplained short stature, pubertal delay, or any constellation of other clinical findings of TS.

NS

- Because negative genetic testing results cannot always rule out NS, a decision about whether to obtain genetic testing relies in part on family preference and the presence or absence of additional features associated with NS (**Table 2**).
- To detect the gene mutations associated with NS
  - DNA sequencing
  - Liquid chromatography
  - Oligonucleotide microarray testing
- If NS is clinically suspected, initial screening for a *PTPN11* mutation is recommended.
- When *PTPN11* mutations are absent, other mutations can be investigated.

IMAGING

- Prenatal imaging
  - Features suggestive of TS found on fetal ultrasonography include polyhydramnios, edema, and increased nuchal fluid.
  - Fetal echocardiography is indicated at 18–20 weeks of gestation if TS is suspected.
  - Polyhydramnios, edema, and increased nuchal fluid on fetal ultrasonography can suggest NS.
  - If NS is suspected during prenatal evaluation, fetal echocardiography is also indicated.

Table 2. Indications for Genetic Testing in Noonan Syndrome

Clinical Presentation	Genetic Testing Considered
Initial presentation of NS phenotype	*PTPN11*
If *PTPN11* Gene Testing Is Negative	
No developmental delays or normal stature	*SOS1*
Hypertrophic obstructive cardiomyopathy	*RAF1*
Significant developmental delays	*KRAS*
Sparse, thin, slow-growing hair	*SHOC2*

Abbreviation: NS, Noonan syndrome.

Adapted from Romano AA, Allanson JE, Dahlgren J, et al. Noonan syndrome: clinical features, diagnosis, and management guidelines. *Pediatrics.* 2010;126(4):746–759.

Table 3. Scoring System for Noonan Syndrome[a]

Feature	A = Major	B = Minor
1. Facial	Typical face dysmorphology	Suggestive face dysmorphology
2. Cardiac	Pulmonary valve stenosis, HOCM and/or ECG typical of NS	Other defects
3. Height	<Third percentile	<10th percentile
4. Chest wall	Pectus carinatum/excavatum	Broad thorax
5. Family history	First-degree relative with definite NS	First-degree relative with suggestive NS
6. Other	Intellectual disability, cryptorchidism, *and* lymphatic dysplasia	Intellectual disability, cryptorchidism, *or* lymphatic dysplasia

Abbreviations: ECG, electrocardiogram; HOCM, hypertrophic obstructive cardiomyopathy; NS, Noonan syndrome.

[a] Definitive Noonan syndrome: 1 A plus 1 other major sign or 2 minor signs; 1 B plus 2 major signs or 3 minor signs.

Adapted from van der Burgt I. Noonan syndrome. *Orphanet J Rare Dis.* 2007;2:1–6. © 2007 van der Burgt; licensee BioMed Central Ltd. http://ojrd.biomedcentral.com/articles/10.1186/1750-1172-2-4#CR2_55. Accessed May 1, 2017.

CLASSIFICATION

- Several clinically based scoring systems have been put in place to help diagnose NS (**Table 3**).

SPECIFIC TREATMENTS

TS

- Growth and endocrine issues
  - Recombinant human GH
    - Consider as soon as growth failure is confirmed.
    - Patients with earlier age at GH initiation and longer duration of GH therapy demonstrated the most benefit.
    - Other advantages of early GH treatment include improvement in peer group integration and age-appropriate estrogen replacement.
  - Oxandrolone
    - Nonaromatizable anabolic steroid with weak androgen effect.
    - Consider in those with a late diagnosis (8–10 years of age); give for ≤4 years as adjuvant therapy for growth promotion.
    - Results in height gain improvement in many, but modest augmentation in height gain in some.
    - Height gain often accompanied by a deceleration in breast development.
- Pubertal delay and hypogonadism
  - ≤30% have some degree of spontaneous puberty.

- Follicle-stimulating hormone (FSH) concentrations are increased in the first 1–2 years of life, followed by a gradual decline in mid- to late childhood.
- In mosaic TS, FSH can be indistinguishable from that of healthy females.
- Estrogen therapy is used to induce development of secondary sexual characteristics, followed by progestin cycling.
- Exact timing of pubertal induction is subject of ongoing study.
- Current recommendation: Consider treatment between 12 and 13 years if spontaneous puberty has not occurred.
- Timely treatment with estrogen can promote bone health and improve psychologic outcomes.
- Forms of estrogen available include oral, transdermal, and injectable.
- Physiologic low-dose replacement is preferable, with gradual increase in dosing, best achieved with transdermally applied estradiol.
- Progesterone is withheld until 18–24 months after estrogen initiation, or when breakthrough menstruation occurs.

■ Neurologic, cognitive, and behavior issues
- Pay careful attention if school performance begins to decline.
- Encourage families to request educational accommodations (eg, extra time to complete homework or examinations).
- Poor social skills and challenges in executive functioning can often lead to and be exacerbated by social isolation.
- Questionnaires provided to adolescents shed light on social anxieties related to delayed puberty and questions surrounding fertility.
  - Be honest when discussing fertility with patients and their families.
  - Alternative means of motherhood, such as adoption, should be explored.
- Psychosexual and vocational counseling may require input from psychologists, educators, and school counselors.

NS

■ Growth and endocrine issues
- GH
  - Approved for use in patients with NS.
  - Initiate in consultation with a pediatric endocrinologist when growth failure is evident.
  - Significant improvement in height SD scores and mean overall height gain (between 9.5 and 13 cm for boys and 9.0 and 9.8 cm for girls).
  - Earlier treatment and longer duration seem to have the most effect.
  - Children with *PTPN11* mutations may respond less favorably to GH therapy than those without such mutations.

■ Cardiovascular issues
- In severe pulmonary valve dysplasia (a subset of pulmonary valve stenosis), a valvectomy or pulmonary homograft is required in childhood.
- Less severe forms of stenosis can be treated with balloon angioplasty.
- Hypertrophic obstructive cardiomyopathy can resolve spontaneously in some NS patients or become rapidly progressive.
- Management includes β-blocker medications and surgical myomectomy to reduce outflow obstruction.
- Regardless of ultimate cardiac diagnosis, lifetime follow-up by a cardiologist is needed.

■ Renal and genitourinary issues
- In males, if cryptorchidism is present, prompt evaluation by a urologist and orchiopexy <1 year are recommended.
- Consultation by a pediatric nephrologist is helpful if hypertension is noted.

■ Pubertal delay/hypogonadism
- Puberty is often delayed in boys and girls with NS and is accompanied by a decreased growth spurt.
- Mean age in boys for onset of puberty is between 13.5 and 14.5 years, and in girls, it is between 13 and 14 years.
- In some instances, puberty may then progress with rapid tempo (<2 years).
- Induction of puberty with appropriate sex hormone replacement can be accomplished in boys at 14 years and girls at 13 years.

■ Neurologic, cognitive, and behavior issues
- Psychiatric or psychological intervention is recommended for NS patients who have poor coping skills, self-injurious behavior, or severe attention-deficit/hyperactivity disorder.

■ Hematologic, orthodontic, and skin issues
- Evaluation by a hematologist is recommended if easy bruising, epistaxis, or menorrhagia is present.
- Orthodontic evaluation is recommended by 7 years of age.

- Lymphedema, excessive nuchal skin, easy bruising, and hyperpigmentation can occur in NS.
- Management of fetal hydrops, pleural effusion, lymphangiectasia, and anomalous lymphatic vessels can be difficult, and follow-up with a lymphedema center is helpful.

WHEN TO REFER

- Endocrinologist: to address growth, pubertal delay, and bone health
- Cardiologist: if cardiac anomalies are present
- Nephrologist: if renal disease is apparent on ultrasonography
- Ear, nose, and throat specialist with an audiologist: to address recurrent otitis and hearing loss
- Developmental pediatrician, psychologist, and mental health professional: for suspected learning, processing, and attention difficulties

FOLLOW-UP

- See tables for suggested tests for monitoring patients with TS (**Table 4**) and NS (**Table 5**).
- Coordinated transition of TS and NS patients from pediatric to adult care physicians has been lacking, especially because multiple subspecialists are involved from an early age.
- Primary care pediatrician must educate young adults about potential medical and psychosocial issues and empower them to proactively pursue care as they mature.
- Provide patients and their families with a medical "passport" in secular language documenting.
  - Medical and surgical history
  - Ongoing medications
  - Advised annual or biannual testing
  - Target weight and blood pressure
  - Data on prior cardiac evaluation and recommendations
- Use a transition coordinator to facilitate movement of data and appointments to adult clinics.
- Use social media, telephone calls, and interactive Web sites to make the transition process more effective.
- For young adults with NS, especially, genetic counseling is appropriate given the autosomal-dominant inheritance pattern.
  - Screening the parents of NS patients for genetic mutations may help assess risk for recurrence.

COMPLICATIONS

TS

- Recommendations for screening and monitoring for complications are seen in **Table 4.**
- Patients with TS are prone to develop autoimmune conditions.
  - Autoantibodies are present in nearly 60%, and 18% of those have >1 organ targeted.
- The incidence of celiac disease is 6%.
  - Screening for tissue transglutaminase should occur by age 4 and every 2–5 years thereafter.
- Cardiovascular issues.
  - Hypertension warrants periodic evaluation for aortic dilation, increasingly by cardiac magnetic resonance imaging.
  - Obesity is common and can complicate treatment for hypertension and result in negative effects on cardiac health.
  - Baseline measurement of fasting glucose, insulin, lipids, and liver enzymes are helpful from 10 years of age, with follow-up testing every 1–2 years and as needed.
- Renal and genitourinary issues.
  - Renal malformations are relatively common, although not always with clinical implications.
  - Horseshoe kidney, ectopy, and malrotation are typical structural abnormalities.
  - Patients with renal defects are more likely to have hypertension.
  - A renal ultrasound should be obtained at diagnosis, with consultation by a pediatric nephrologist if the findings are abnormal.
- Vision and hearing
  - Structural eye abnormalities (downward sloping palpebral fissures, ptosis, and epicanthal folds).
  - Strabismus and hyperopia have been reported in ≤30% of patients.
  - Initial ophthalmologic evaluation is recommended between 1 and 2 years of age.
  - Maintain a high level of suspicion for otitis media.
  - Light otoscopy and pneumatic tympanometry are useful until at least 7 years of age.
  - If hearing loss or chronic ear infections are present, yearly audiology examinations and referral to an audiologist are recommended.
  - For those without documented hearing loss or chronic otitis, similar examinations can take place every 2–3 years.

Table 4. Screening and Monitoring for Turner Syndrome

Age	Screening at Diagnosis	Ongoing Monitoring
All patients	Cardiology consultation Renal ultrasonography Audiology evaluation Examination for scoliosis/kyphosis Discussion of aspects of TS Support group referral Evaluation of progress of growth and pubertal development	Cardiology follow-up and evaluation as indicated Annual blood pressure check Reevaluation by ENT/audiology physician every 1–5 y Growth evaluation
0–4 y	Hip examination for congenital hip dislocation Pediatric ophthalmology examination (>1 y)	Social skills evaluation at 4–5 y
4–10 y	Thyroid function testing (T_4, TSH) Celiac screen (tTG Ab) Educational/psychosocial assessment Orthodontic evaluation (>7 y)	Liver/thyroid screening yearly Celiac screen every 2–5 y Yearly education/social progress evaluation Dental/orthodontic evaluation as needed
>10 y	Thyroid function testing (T_4, TSH) Celiac screen (tTG Ab) Educational/psychosocial assessment Ovarian function evaluation Begin estrogen replacement when appropriate Liver function testing, fasting blood glucose, CBC, renal function testing Bone mineral density (>18 y)	Fasting lipids/blood glucose yearly Liver/thyroid screening yearly Celiac screen if clinically indicated Evaluation of pubertal development and psychosocial development at age-appropriate times

Abbreviations: Ab, antibody; CBC, complete blood cell count; ENT, ear, nose, and throat; T_4, thyroxine; TS, Turner syndrome; TSH, thyroid-stimulating hormone; tTG, tissue transglutaminase.

Adapted from Loscalzo ML. Turner syndrome. *Pediatr Rev.* 2008;29(7):219–227; and Bondy CA; Turner Syndrome Study Group. Care of girls and women with Turner syndrome: a guideline of the Turner Syndrome Study Group. *J Clin Endocrinol Metab.* 2007;92(1):10–25.

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NS

- Recommendations for screening and monitoring for complications of NS are seen in **Table 5.**
- Hearing loss.
  - Light otoscopy with pneumatic tympanometry is useful until at least 7 years of age.
  - If hearing loss is identified or ear infections persist, yearly hearing examinations and referral to an audiologist are recommended.
  - For those without documented hearing loss or chronic otitis, screening audiology is done every 2–3 years.

Table 5. Screening and Monitoring for Noonan Syndrome

Clinical Specialty Issue	Recommendations
Cardiovascular	Evaluation by cardiologist at time of diagnosis, including echocardiogram and electrocardiogram Regular follow-up if defect present Interval follow-up every 5 y if no defect present
Growth and endocrine	Weight and height measurements regularly by primary physician Evaluation by an endocrinologist if growth deceleration, height ≤2 SD, or delayed puberty Thyroid testing if goiter present
Renal and genitourinary	Renal ultrasonography at time of diagnosis Consider antibiotic prophylaxis with hydronephrosis or recurrent urinary tract infection. Orchiopexy performed by age of 1 y if cryptorchidism present
Gastrointestinal	Evaluation by gastroenterologist for feeding difficulties or persistent vomiting
Hematology	Screening CBC with differential, PT, and aPTT at diagnosis and after 6–12 mo of age If bleeding, first obtain CBC, PT, and aPTT; then evaluate specific clotting factor activity in consult with hematologist. Preoperative evaluation for all surgeries by hematologist
Cognitive and behavioral	Developmental screen annually Complete neuropsychiatric testing if abnormal. Evaluations by physical therapist, occupational therapist, and speech therapist if delayed, with earliest intervention possible Individual education plans updated yearly with schools Evaluation by neurologist if seizures suspected Brain and upper spine MRI with any neurologic problem Consider MRI angiogram if sudden focal findings.
Eye and ear	Detailed eye examination at diagnosis Eye reevaluation as indicated if problems or at least every 2 y thereafter Hearing testing in infancy or at diagnosis with regular testing in childhood
Orthopedic	Annual examination of chest and back; radiography if abnormal
Orthodontic	Dental referral between 1 and 2 y of age Careful oral examination at each visit
Lymphatic	Referral to specialty lymphedema clinic if possible For more information, contact National Lymphedema Network.

Abbreviations: aPTT, activated partial thromboplastin time; CBC, complete blood cell count; MRI, magnetic resonance imaging; PT, prothrombin time; SD, standard deviation.

Derived from Romano AA, Allanson JE, Dahlgren J, et al. Noonan syndrome: clinical features, diagnosis, and management guidelines. *Pediatrics.* 2010;126(4):746–759; and Lee BH, Kim JM, Jin HY, Kim GH, Choi JH, Yoo HW. Spectrum of mutations in Noonan syndrome and their correlation with phenotypes. *J Pediatr.* 2011;159(6):1029–1035.

DEFINITION

- Urinary tract infection (UTI) is a common childhood infectious disease.

SIGNS AND SYMPTOMS

History

- Clinical presentation of UTI depends on
  - Age of the child
  - Virulence of underlying pathogen
  - Inflammatory response of the host
- Symptoms most often associated with UTI include
  - Dysuria
  - Frequency
  - Urgency
  - Lower back pain
- Symptoms of UTI are variable and nonspecific in young children, especially infants.
- Bacteremic UTI can be clinically indistinguishable from other types of infection in very young children.
- Small children usually cannot
  - Localize pain.
  - Report precise symptoms.
  - Some parents can detect symptoms suggestive of UTI in these children.
- By 4 years, children's capability improves to report more specific symptoms.
  - Abdominal pain
  - Dysuria
- In children >5 years, classical symptoms of UTI may be present.
  - Urgency
  - Frequency
  - Dysuria
- Fever is the most prominent and, often, the only clearly recognized sign of UTI in children.
  - In newborns, normal body temperature does not exclude the possibility of upper UTI.
- With some caveats, fever can be used as a rough estimate of the level of UTI.
  - Body temperature <38.0°C (100.4°F) suggests cystitis.
  - Temperature ≥38.5°C (101.3°F) most often is associated with upper UTI.

Physical Examination

- Findings vary depending on severity of the infection.
- In infants, findings are nonspecific and rarely definitive.
- Fever is an important sign in infants and children <2 years.
- In addition to fever, other findings suggestive of septicemia can be seen in young infants, including
  - Irritability
  - Abnormal crying
  - Peripheral cyanosis
  - Hypothermia
  - Prolonged capillary filling time
- Tenderness on palpation of the abdomen in the suprapubic region can be found with cystitis.
- Costovertebral angle tenderness is elicited in older children with pyelonephritis.
- An absence of typical findings does not rule out the possibility.
- Examination of the urethral meatus should be included in the examination of every child with suspected UTI.
- In some cases, dysuria can be caused by local inflammation or irritation of external genitalia.
  - External genitalia in girls should be examined carefully.
  - Labial adhesions are often associated with UTI.

DIFFERENTIAL DIAGNOSIS

- UTI should be included in the sepsis workup of seriously ill infants and younger children.
- UTI should always be considered as a possible cause of unexplained fever.
- Fever can be an inconsistent finding.
  - In newborns, normal body temperature does not exclude the possibility of upper UTI.
  - Fever exists in only ~10%–40% of UTI cases in children <2 years.
  - In these cases, other symptoms should be considered as indications for urine screening.
    - Vomiting
    - Irritability
    - Abnormal crying
    - Lethargy
    - Failure to thrive
    - Feeding problems

DIAGNOSTIC APPROACH

- UTI should be suspected in infants and young children with unexplained fever.
- Thoroughly assess
  - Degree of toxicity
  - Dehydration
  - Ability to retain oral intake
- If child is critically ill, a urine specimen should be obtained by
  - Catheterization
  - Suprapubic percutaneous aspiration

- If the urinalysis suggests UTI, repeat urine collection by
  - Catheterization
  - Suprapubic aspiration
- Correct diagnosis is crucial for successful treatment and follow-up of childhood UTI.
  - Incorrect diagnosis of UTI may lead to
    - Missing a potentially harmful urinary tract abnormality
    - Unnecessary studies, costs, and stress
- UTI must be always confirmed by adequate urine collection and culture.

LABORATORY FINDINGS

Urine Collection

- Adequate urine collection is essential for correct diagnosis.
  - To prevent contamination, all samples should be carefully collected, stored, and analyzed.
    - Sample collection at home is discouraged because of the high risk of contamination.
    - Urine samples should be kept at 4.0°C (39.2°F) until cultured unless cultured ≤1 hour of voiding.
- If a febrile child with suspected UTI cannot provide a clean-catch urine specimen, the specimen should be obtained through catheterization or suprapubic aspiration before antimicrobial treatment is started.
- The diagnosis cannot be established reliably through culture of urine collected in a bag.
- Toilet-trained children and adolescents.
  - Midstream urine sample is preferred for culture.
  - Before micturition, the periurethral area and surrounding skin should be washed and dried.
  - When sample is obtained through bladder catheterization or voiding, the first few drops should be allowed to fall outside the sterile container, to avoid being contaminated by bacteria in the distal urethra.
    - Cultures of urine samples collected via bag applied to the perineum have very high false-positive results.
- Incontinent children.
  - Use of a urine bag or absorbent pad for urine collection should be avoided.
    - Urine contamination rates are similar for bag and pad (75% of positive culture results).
  - A negative culture result from urine collected by bag or pad excludes UTI.
  - A positive culture result from a urine bag or urine pad sample should always be verified by
    - Catheterization
    - Suprapubic aspiration
- Guidelines for suprapubic percutaneous aspiration.
  - Indications
    - Verification of UTI in newborns and infants
    - Sepsis workup in critically ill children
  - Equipment
    - 21- to 25-gauge needle
    - 5- to 10-mL syringe
    - EMLA cream
    - Sterile gloves
    - Portable ultrasonography equipment
  - Technique
    - Ensure that there is urine in the bladder, optimally with ultrasound.
      - Alternatively, careful observation that the child has not voided for at least 45–60 minutes.
    - Put a small amount of EMLA cream on a circle area (~3 cm) ~2–3 cm above symphysis midline.
    - Wait ~30 minutes.
    - Set the child in a supine position.
    - Clean the patient's skin with antiseptic solution.
    - Insert the needle percutaneously at ~1 fingerbreadth above the symphysis pubis.
    - Advance slowly with continuous suction.
    - Usually urine is obtained at a depth of 2–3 cm.
  - Complications
    - Generally safe and reliable with an experienced operator
    - Occasionally transient hematuria (2%–3%)
    - Intestinal puncture not harmful
- Transurethral bladder catheterization.
  - Restrain child in supine and frog-leg position for adequate stabilization of the pelvis and complete visualization of external genitalia.
  - Cleanse the anterior urethra thoroughly with povidone-iodine solution.
  - Apply a sterile lubricant jelly to the end of an appropriately sized catheter.
  - Urinary catheter sizes recommended by age.
    - 5F for infants <6 months
    - 8F for those between 6 months and adolescence
    - 10F for adolescents
  - If a topical anesthetic is used, it should be applied 2–3 minutes before the procedure.

- However, the efficacy of using topical lidocaine to reduce pain during urethral catheterization in children remains uncertain.
- Boys
  - In uncircumcised males, retract foreskin of the glans gently to permit complete visualization of the urethral meatus.
  - Straighten urethra by using the nondominant hand to hold the penis perpendicular to the lower abdomen and apply gentle traction.
  - Insert catheter with the dominant hand until urine returns.
  - Advance catheter and continue to palpate along the posterior aspect of the penis.
  - Maintain traction on the penis, while applying gentle pressure with the catheter.
  - Catheter should never be forced.
  - Reduce foreskin to its normal position so that a paraphimosis does not develop.
- Girls
  - Urethra may be difficult to visualize, and an assistant often is needed to retract labia majora.
  - Have the assistant lift labia majora anteriorly, laterally, and cephalad.
  - Swab the area from front to back; this may help push this tissue out of the way and permit the povidone-iodine solution to pool in the meatus, making identification easier.
    - Insert catheter into the urethral meatus until urine returns.
    - Discard first few drops of urine obtained to prevent contamination.
      - This will help decrease the false-positive results on urinalysis for white blood cell counts and bacteria detection.

Urine Culture

- Diagnosis is confirmed by the growth of a single pathogen on urinary culture and significant pyuria on urinalysis.
- American Academy of Pediatrics (AAP) UTI guidelines consider counts >50,000 colony-forming units (CFU)/mL diagnostic for UTI.
- The bacteria level considered significant depends on the method used for urine collection.
  - For voided samples (clean-catch urine, urine bag, and absorbent pad)
    - Bacterial count ≥100,000 CFU/mL is considered significant.
    - Bag and absorbent pad cultures are not accurate and must be confirmed.
  - Contamination risk for catheterization and suprapubic aspirate is considerably lower.
    - Any bacterial growth in suprapubic aspirate or a bacterial count ≥50,000 CFU/mL in a catheter sample is indicative of UTI.
- If signs and symptoms strongly suggest UTI
  - Lower bacteria counts (≥10,000 CFU/mL), particularly in the presence of pyuria, may be considered diagnostic.
- Urine cultures showing growth of ≥1 pathogen should be considered contaminated; a repeat sample is required before starting any treatment.

Urinalysis

- Urinalysis by itself is not sufficient to diagnose UTI.
- Results of urine culture usually are not available on the same day the sample is collected.
- Urinalysis showing leukocyturia can support diagnosis of UTI.
  - Leukocytes may be present in urine (pyuria) for other reasons.
  - Pyuria is defined as ≥10 leukocytes/mcL in an uncentrifuged urinary specimen.
    - A count <10 leukocytes/mcL is almost invariably associated with a sterile urine culture.
    - A count ≥10 leukocytes/mcL is found in 90% of patients with bacterial growth ≥50,000 CFU/mL.
  - The dipstick leukocyte esterase test has a sensitivity of ~83% when used in clinically suspected UTI.
- High urinary leukocyte count is very sensitive (~95%) but not specific for the presence of a UTI.
- UTI can be an important cause of microscopic hematuria.
  - The presence of erythrocytes in urine does not have diagnostic or prognostic value.
- The combination of cell count and Gram stain can be
  - More sensitive (87.7%)
  - More specific (99.2%)
- A positive leukocyte esterase or a positive nitrate result is highly suggestive of a UTI.
  - Sensitivity of 93%
  - Specificity of 72%
- Combination of leukocyte esterase test and a positive nitrite test
  - Does not improve sensitivity (78.7%)
  - Increases specificity (98.3%)

- A combination of cell counts and Gram stain has more sensitivity (87.7%) and specificity (99.2%) when assessing the risk for UTI.
- Combining the leukocyte esterase test plus a nitrite test or urine microscopy significantly increases sensitivity (99.8%).
- The nitrite test result is usually positive if bacterial counts are high enough (>100,000 CFU/mL).
  - Chemical reaction (conversion of nitrates to nitrites) requires that urine be present in the bladder for at least 4 hours.
  - Only ~50% of UTIs will feature a positive urine nitrite test result.

Determining Location of UTI

- Reliable differentiation of upper UTI from lower UTI can be difficult.
- Pyelonephritis is suggested by
  - Temperature ≥38.5°C (101.3°F).
  - Increased C-reactive protein level (≥40 mg/L).
  - Leukocytosis.
  - Infants may have afebrile bacteremic UTI.
- Several biomarkers are currently being evaluated as possible indicators of upper UTI.
  - Procalcitonin.
    - Recently proposed as a possible indicator of pyelonephritis.
    - Increased serum procalcitonin levels correlate significantly with renal parenchymal involvement in children with febrile UTI.
  - No correlation between level of UTI and serum electrolyte, creatinine, and blood urea nitrogen concentrations has been reported.
  - These parameters should be measured to assess level of hydration or other attendant complications in
    - Infants <12 months
    - Patients with febrile UTI
    - Patients with associated symptoms, such as vomiting or diarrhea

IMAGING

General

- Imaging studies of the urinary tract are no longer recommended for all children with a first-time UTI but should be for high-risk patients.
  - The highest risks for significant urinary tract abnormalities are in infants <1 year and in children with non–*Escherichia coli* UTI versus those with *E coli*–associated UTI.
- Imaging studies of the urinary tract are recommended to exclude anatomic abnormalities in the kidney or urinary tract.
  - Obstructive disorders
  - Vesicoureteral reflux (VUR)
- Imaging studies used in UTI include
  - Renal and bladder ultrasonography (RBUS)
  - Voiding cystourethrography (VCUG)
  - Technetium Tc 99m dimercaptosuccinic acid (DMSA) scan

Indications

- RBUS.
  - Infants and children 2–24 months with first-time febrile UTI.
  - Atypical UTI, all ages.
  - Recurrent UTI, all ages.
  - If fast clinical improvement is achieved, RBUS can be delayed until full recovery.
  - If no clear response to treatment in ≤48 hours, acute RBUS to identify complications such as renal and perirenal abscesses and pyonephrosis.
- VCUG.
  - In infants and children 2–24 months when RBUS reveals hydronephrosis, scarring, or other findings suggesting high-grade VUR or obstruction of the urinary tract.
  - First-time febrile UTI, abnormal RBUS, complex clinical circumstances, and age 2–24 months.
  - Positive family history of VUR.
  - Prenatal detection of urinary tract dilatation.
  - History of complicated or recurrent pyelonephritis.
  - Atypical UTI and age <6 months.
  - Recurrent UTI and age <6 months.
  - When indicated, VCUG can be done within a week of diagnosis.
- DMSA scan.
  - Atypical UTI and age <3 years
  - Recurrent UTI, all ages
- AAP recommends that children <2 years with first-time UTI should be studied by
  - Ultrasonography in the acute phase
  - Cystography or renal cortical scan thereafter as soon as possible
- Infants and children who do not demonstrate expected clinical response ≤2 days of antimicrobial therapy should promptly undergo ultrasonography.
  - At the earliest convenient time, perform
    - VCUG *or*
    - Radionuclide scan

- Infants and young children who have expected response to antimicrobials should have
  - Ultrasonography
  - At the earliest convenient time
    - VCUG *or*
    - Radionuclide scan
- The optimal time for VCUG is ~2–6 weeks after infection.
- Recommendations about imaging studies after UTI in older children are
  - More variable
  - Dependent on clinical presentation
- The probability of factors predisposing patient to renal damage is relatively low in children >2 years.
  - Imaging studies are recommended in this age group in the following scenarios:
    - Recurrent UTI
    - Non–*E coli* infection
    - Positive family history

RBUS

- Least invasive, most widely available imaging modality.
- Can be performed during the acute phase of UTI.
- Can detect
  - Dilated collecting system
  - Thinning of kidney parenchyma
  - Size of kidneys
  - Thickness and size of urinary bladder
- May not be able to detect
  - VUR
  - Smaller renal scars
- Reliability is highly dependent on the experience of the ultrasonographer.
- Recent studies suggest that results may have little or no influence on treatment because of routine prenatal ultrasonography.
  - The need for ultrasonography after UTI has been questioned.
  - Widespread use of maternal-fetal ultrasonography in industrialized countries has possibly lessened the need for ultrasonography later in childhood.
  - Several studies have shown that a significant kidney or urinary tract abnormality may be missed despite prenatal RBUS in 5%–6% of children with first-time febrile UTI.

VCUG

- Traditionally used to diagnose VUR because VUR
  - Predisposes patients to pyelonephritis and recurrent infections.
  - May be associated with renal scarring.
  - Incidence is highest in children <2 years.
- VCUG can be performed using
  - Radiocontrast medium
  - Radiolabeled nuclides
- Contrast VCUG is usually preferred in boys.
  - More reliable than other methods in detecting urethral valves
  - Recommended as a baseline study in all children with first-time UTI
  - Allows more exact grading of reflux
- Isotope VCUG is recommended for follow-up studies.
- Cystography.
  - Requires catheterization, which is relatively invasive and stressful, especially in older children.
  - Exposes children to radiation and is relatively laborious and costly.
  - Recent evidence suggests that a low-grade VUR (grade <3) itself is not a significant risk factor for renal damage and that antimicrobial prophylaxis is not effective in preventing renal damage in children with VUR.
  - For these reasons, the use of cystography has dramatically decreased in recent years.
  - Current AAP recommendation.
    - VCUG should not be performed on a routine basis after a first febrile UTI.
    - VCUG should be performed in infants and children 2–24 months if RBUS shows evidence of hydronephrosis, scarring, or other findings that would suggest high-grade VUR or obstructive uropathy.
    - National Institute for Health and Care Excellence (NICE) guideline from the United Kingdom
      - Restricts cystogram only to infants <6 months with atypical UTI (eg, dilatation on ultrasound, poor urine flow, non–*E coli* infection, family history of VUR)
- Should be considered for children presenting with complex clinical circumstances.
- Spontaneous resolution of VUR occurs in a high proportion of children.
  - Isotope VCUG is recommended every 1–3 years until resolution of VUR is documented.

DMSA Scan

- One of the most reliable methods to differentiate pyelonephritis from lower UTI.

- Radionuclide is taken up by renal tubular cells and provides information on
  - Functional anatomy
  - Scarring of renal parenchyma
- More often abnormal in patients with documented reflux than in children without VUR.
- Some (including the authors of the NICE clinical guideline) suggest that the DMSA scan should be performed
  - 4–6 weeks following the first-time UTI in all children <3 years with atypical UTI or recurrent UTIs
  - In children >3 years with recurrent UTIs
- Recurrent UTI has been defined as
  - ≥2 episodes of upper UTI *or*
  - 1 episode of upper UTI plus ≥1 episodes of lower UTI *or*
  - ≥3 episodes of lower UTI.
  - This approach has likely reduced the number of VCUGs performed by ~50% without adding any major risk.
- AAP guideline does not recommend a routine DMSA scan after the first UTI in children.
- Only 55%–85% of children with febrile UTI have changes on radionuclide studies, such as DMSA scan.
  - Suggested as a gold standard for diagnosing pyelonephritis

CLASSIFICATION

- International classification of VUR
  - Grade I: involves only ureters
  - Grade II: involves ureters and intrarenal collecting systems
  - Grade III: mild ureteral and pelvic dilatation; no or slight obliteration of caliceal fornices
  - Grade IV: moderate ureteral and pelvic dilatation; clear obliteration of caliceal fornices
  - Grade V: gross dilatation of ureters and renal pelvis and calyces

TREATMENT APPROACH

- Initial antibiotics should be administered parenterally if the child with suspected UTI is
  - Septic
  - Dehydrated
  - Unable to retain oral intake
- Antibiotic therapy should be initiated parenterally or orally in a child who
  - May not appear ill
  - Has a urine culture confirming presence of UTI
- Reevaluate infants and children who do not demonstrate expected clinical response within 2 days of antimicrobial therapy.
- Infants and young children should complete a 7- to 14-day antimicrobial course.
- After antimicrobial therapy and sterilization of urine
  - Infants and young children should receive prophylactic antimicrobial doses until the imaging studies are completed.

SPECIFIC TREATMENTS

General

- Successful treatment includes
  - Early recognition
  - Early, appropriate treatment
- Before initiating treatment, adequate samples of urine should be collected for
  - Culture
  - Antibiotic sensitivities of organisms
- If the patient is septic or dehydrated
  - Adequate rehydration should coincide with antibiotic therapy.
- Route of antibiotic administration (oral or parenteral) depends on
  - Age
  - Clinical condition of patient

Pyelonephritis

- Infants <1 year.
  - Hospitalize.
  - Treat with parenteral antibiotics for ≥3 days.
  - Follow by oral antibiotic therapy for 11 days (total of 14 days).
- Research has shown that oral antibiotics are as effective as parenteral antibiotics, even in young children with febrile UTI.
  - If child does not appear septic and can tolerate oral medications
    - Initial treatment with oral antibiotic might be appropriate.
    - Follow-up is essential to ensure complete recovery.
- Infants <2 months should be hospitalized in all instances.

Cystitis

- Oral therapy alone is usually adequate to treat cystitis, assuming adequate liquid intake and an ability to tolerate antibiotics.
- First-line therapy for outpatient treatment of UTI.
  - Amoxicillin plus clavulanic acid *or*
  - Cephalosporin *or*
  - Trimethoprim-sulfamethoxazole (TMP-SMX)

- It is important to know the sensitivity patterns of common UTI-causing organisms in a given geographic area to select the most effective initial agent before sensitivity results are available from urine culture.
- 5 days of treatment with appropriate antibiotics is adequate for children <2 years who are afebrile and have uncomplicated cystitis.

Asymptomatic Bacteriuria (ABU)

- Studies on infants and school-aged girls have shown that untreated ABU does not increase the risk for
  - Pyelonephritis
  - Renal damage
- Children treated with antibiotics for ABU can have a higher incidence of pyelonephritis than untreated children.
- Researchers have suggested that pathogens causing ABU have low virulence and may protect against overgrowth of uropathogenic bacteria.
- Current recommendations are
  - Should not be treated with antibiotics in
    - Children who use intermittent catheterization
    - Children with neurologic bladder dysfunction
  - These children frequently have ABU.
    - Asymptomatic
    - Often do not have leukocyturia

Antibiotic Dosing

- Parenteral therapy
  - Ampicillin
    - 100 mg/kg/d divided every 6 hours
  - Amikacin
    - 15.0–22.5 mg/kg/d divided every 8 hours
  - Ampicillin-sulbactam
    - 100–200 mg/kg/d ampicillin divided every 6 hours
  - Cefepime
    - 100–150 mg/kg/d divided every 8 hours
  - Cefotaxime
    - 100–150 mg/kg/d divided every 8 hours
  - Ceftazidime
    - 100–150 mg/kg/d divided every 8 hours
  - Gentamicin
    - 5.0–7.5 mg/kg/d divided every 8 hours
  - TMP-SMX
    - 8–12 mg/kg/d TMP with 40–60 mg/kg/d SMX divided every 12 hours
- Enteral therapy
  - Amoxicillin
    - 30–40 mg/kg/d divided every 12 hours
  - Amoxicillin-clavulanate
    - 30 mg/kg/d divided every 12 hours
  - Cefixime
    - 8–16 mg/kg/d once daily or divided every 12 hours
  - Cephalexin
    - 40–50 mg/kg/d divided every 6–8 hours
  - Cefpodoxime
    - 10 mg/kg/d divided every 12 hours
  - Methenamine mandelate
    - 40–50 mg/kg/d divided every 8–12 hours
  - Nitrofurantoin
    - 5–7 mg/kg/d divided every 6 hours
  - Sulfisoxazole
    - 150 mg/kg/d divided every 6 hours
  - TMP-SMX
    - 6–12 mg/kg/d TMP with 10–60 mg/kg SMX divided every 8–12 hours

WHEN TO ADMIT

- Suspected urosepsis
- Infant <3 months with UTI
- Suspected UTI in a dehydrated patient or a patient who cannot retain oral fluids
- Patients whose symptoms worsen or do not improve despite oral treatment

WHEN TO REFER

- Abnormal findings on imaging
- Frequently relapsing UTI
- Suspicion of voiding dysfunction
- Renal insufficiency (elevated creatinine)
- Hypertension

FOLLOW-UP

- Patients with VUR
  - Prophylactic antibiotics should be continued.
  - Regular follow-up.
  - Repeat VCUG to determine the status of VUR.

COMPLICATIONS

- Association of anatomic abnormalities in the kidneys or in the urinary tract is increased in children with UTI.
  - Risk is higher in children with non–*E coli* UTI.
- Incidence of complications after UTI can be dramatically reduced by
  - Thorough radiologic investigation of young children with UTI

- Appropriate treatment
- Follow-up

- Renal scarring.
  - Isotope uptake studies (DMSA scans) have shown that the renal parenchyma is affected in ~55%–75% of children with febrile UTI.
    - ~15%–40% of these children will develop permanent renal parenchymal damage (renal scarring).
  - In some cases, renal disease may be congenital rather than acquired and not dependent on UTI.
  - VUR is a major determinant of the development of renal scars.
  - In a recent meta-analysis of 33 published studies, of all children with an initial episode of UTI
    - 57% had changes consistent with acute pyelonephritis on the acute-phase DMSA renal scan.
    - 15% had evidence of renal scarring on the follow-up DMSA scan.
    - Children with VUR were significantly more likely to develop pyelonephritis (relative risk [RR]: 1.5 [95% CI: 1.1–1.9]) and renal scarring (RR: 2.6 [95% CI: 1.7–3.9]) compared with children with no VUR.
    - Children with VUR grades ≥III were twice as likely as children with lower grades of VUR to develop scarring.
  - In an analysis of 1,221 children with first-time UTI, the incidence of permanent renal damage was
    - 86% in boys
    - 30% in girls
  - The mean age of boys at the time of UTI was significantly lower compared with girls.
  - VUR was present in
    - 67% of boys (higher incidence of congenital renal disease and damage to the kidney parenchyma)
    - 19% of girls (renal damage is acquired and results from UTI)
  - Infants (mean age 4 months) with high-grade VUR without UTI have fewer scars than patients with VUR with a history of UTI.
  - It may be difficult to determine the exact cause of renal dysfunction in children with high-grade VUR, UTI, and renal damage.
  - Contributing factors include congenital factors, reflux, and infection.
  - Risk factors for renal parenchymal damage include
    - Gross VUR
    - Young age at the time of first infection
    - Delayed initiation of treatment
    - Recurrent infections
- Long-term effects of UTI.
  - If no renal abnormalities are found in imaging studies performed after a first childhood UTI, it appears unlikely that subsequent childhood UTIs will cause chronic kidney disease later in life.
  - Most children with UTIs have no long-term consequences.
  - Sequelae that can be associated with UTIs include
    - Small risk of permanent renal damage.
      - May increase risk of hypertension
      - May ultimately cause varying degrees of renal failure
    - Increased risk of preeclampsia during pregnancy.
    - Risk for end-stage kidney disease is relatively small in children without structural anomalies with UTI.
    - According to the North American Pediatric Renal Trials and Collaborative Studies
      - Pyelonephritis (without known structural disease) or interstitial nephritis accounts for renal failure in only 1.8% of all patients who require renal transplantation.
      - Obstructive uropathy accounts for renal failure in 16.1%.
      - Renal hypoplasia or dysplasia accounts for renal failure in 16%.
      - Reflux nephropathy accounts for renal failure in 5.2%.
    - Anatomic abnormality with or without UTI is a more important threat for kidney function than UTI itself.
    - Hypertension remains an uncommon and important long-term complication of childhood UTI.
      - Incidence may be lowered by careful attention to risk factors and early treatment.
    - Bacteriuria and symptomatic UTI are significantly more common in pregnant women with a history of childhood UTI.
    - UTI may contribute to increased risk for preeclampsia (hypertension and proteinuria).

PREVENTION

Prophylaxis

- Prophylactic antibiotics are no longer recommended for all children after their first UTI.
  - Low-dose antimicrobial treatment does not necessarily reduce the number of recurrent infections or protect against renal scarring.
  - Prolonged use of antimicrobials may lead to development of bacterial resistance.
- Prophylaxis should be considered for children with an increased risk of UTI.
  - Children with higher grades of VUR (grades III–V)
  - Children with bowel and bladder dysfunction, obstructive uropathy, and a history of UTI
  - Children with recurrent UTIs (3 febrile UTIs/6 mo or 4 total UTIs/y)
- The most common prophylactic regimen is
  - Co-trimoxazole (TMP-SMX [2 mg/kg TMP with 10 mg/kg/d SMX once every night]) *or*
  - Nitrofurantoin (1–2 mg/kg/d) as a single daily bedtime dose
- Duration of prophylaxis depends on indication.
- In children with VUR, prophylaxis is usually continued until
  - Reflux has resolved spontaneously or has been surgically corrected.
  - The child has been free of symptoms and bacteriuria for ≥1 year.
- Dosing for prophylaxis.
  - Amoxicillin
    - 10–15 mg/kg once daily at bedtime
  - Amoxicillin-clavulanate
    - 25 mg/kg once daily at bedtime
  - Cephalexin
    - 12–15 mg/kg once daily at bedtime
  - Nitrofurantoin
    - 1–2 mg/kg once daily at bedtime
  - Sulfisoxazole
    - 50 mg/kg once daily at bedtime
  - TMP-SMX
    - 2 mg/kg TMP with 30–60 mg/kg SMX divided every 8–12 hours

Supplemental Therapy

- Constipation and encopresis are known to be risk factors for UTI.
- Treatment of these problems is important to prevent recurrent UTI by
  - Dietary modification
  - Medication
- The role of circumcision in preventing UTI has been studied.
  - Relative risk of UTI in uncircumcised male infants compared with circumcised male infants is increased from 4-fold to as much as 10-fold during the first year of life.
  - Absolute risk of UTI in an uncircumcised male infant is low (at most, ~1%).
  - Currently, data are not sufficient to recommend routine neonatal circumcision.

HISTORY

- A complete history with a thorough physical examination will provide important clues to the diagnosis of vaginal bleeding.

Prepubertal Girls

- A careful, nonthreatening history from the child and caregiver if there is any suggestion of sexual abuse
  - May determine the need for referral to child protective services for a forensic interview and subspecialty medical evaluation
- History of pruritus
  - From irritants or infection leading to excoriations
  - Nighttime pruritus suggestive of pinworm infestation
- History of trauma
  - For example, a straddle injury during bicycle riding
- History of foreign body placement
- Family history of coagulopathy

Pubertal Girls

- Maternal support during the initial history taking can be useful.
  - Many mothers track the menstrual periods of adolescent daughters, especially in the first years after menarche, and are keenly aware of
    - Quantity of bleeding based on the quantity of feminine products purchased and stained laundry
    - Evidence of fatigue
    - General activity level and behavior
  - A mother can often provide detailed family medical histories for
    - First-degree female relatives
    - Her daughter
- Key aspects of the history may be difficult to obtain (ie, sexual intercourse or sexual abuse).
- The patient should be interviewed alone about
  - Sexual activity
    - Occasionally, a small amount of bleeding or spotting may follow sexual intercourse.
  - Sexually transmitted infections (STIs) and associated symptoms, such as
    - Cramping
    - Vaginal discharge
    - Dyspareunia
  - Abuse
  - Stress
  - Weight changes and eating habits
  - Participation in sports and other activities
  - Chronic illnesses
  - Other bleeding problems
  - Medication use (particularly contraceptives)
  - Substance use
- Menstrual pattern.
  - Is there bleeding between normal periods?
  - Have previously regular menses become more frequent or heavier?
    - A teenager whose prior menses have been regular might begin to have infrequent but heavy menstrual bleeding.
  - Likelihood of a coagulopathy or another pathologic condition is increased by
    - Heavy bleeding at menarche
    - Significant anemia
    - Need for hospitalization to control the bleeding
- In general, typical periods in adult women are
  - Measured from the first day of one period to the first day of the next.
  - Range of 21–35 days.
  - Flow of 3–7 days.
  - Flow >1 week is considered excessive.
- A similar cycle pattern is observed in adolescent girls.
  - Cycle length is more variable, especially in the first few years after menarche.
  - Some women will have spotting around the time of ovulation.
- Normal blood loss during menses.
  - 30–40 mL.
  - Upper limit of 80 mL.
  - Quantity of blood loss is difficult to assess by history unless the patient reports very light flow.
  - The patient should describe the number of pads or tampons used.
  - Research has demonstrated the value of pictorial assessment to determine menstrual blood loss.
- Changes related to hormonal contraceptive use.
  - Bleeding between periods is common during the first 2 or 3 cycles of oral contraceptive use.
  - Teenagers who forget to take 1 or 2 oral contraceptive pills may experience bleeding.
  - Medroxyprogesterone acetate (Depo-Provera) injections.
    - Associated with frequent and irregular periods of excess bleeding, particularly in the first months after beginning use
- Complete family history.
  - Important to determine whether other family members have any kind of bleeding problem.
  - Family history is a better predictor of coagulopathy than menstrual history.

PHYSICAL EXAMINATION

- Make sure that the bleeding is vaginal in origin.
  - A prolapsed urethra can mimic vaginal bleeding.

Prepubertal Girls

- Any suggestion of sexual abuse
  - Bruises
  - Hymenal tears
  - Other signs of trauma
    - The most common finding after sexual abuse is a typical examination without evidence of trauma.
- Excoriations, erythema, or a rash in the perineal area
  - Vulvovaginitis is a possibility.
  - Pruritus from an irritant.
  - If nighttime pruritus, may indicate a pinworm infestation.
- Bruising
  - From trauma
  - With multiple bruises and petechiae, possible coagulopathy
- Foreign body in the vagina
  - Should always be considered, even if no history of such exists
- Abnormal lesions
  - Hemangiomas
  - Condylomata
  - Tumors

Pubertal Girls

- Typical findings help rule out many causes of vaginal bleeding or abnormal uterine bleeding.
  - Height
  - Weight
  - Blood pressure
  - Thorough palpation of the thyroid gland
  - Pelvic examination
  - Fundoscopic and visual fields examinations to exclude prolactinoma
- Endocrine disorders are indicated by
  - Increased facial hair
    - Polycystic ovaries
    - Adrenal tumor
  - Cold intolerance
    - Hypothyroidism
  - Polyuria
    - Pituitary tumor
  - Nipple discharge
    - Hyperprolactinemia
  - Headache
    - Pituitary tumor
  - Acne
    - Polycystic ovaries
    - Adrenal tumor
  - Striae
    - Cushing disease
  - Enlarged clitoris
    - Androgen-secreting tumor
    - Late-onset 21-hydroxylase deficiency
- Vulvar or vaginal bruising or lacerations.
  - Probable sexual abuse
- Lack of abdominal pain with adnexal or cervical motion tenderness.
  - Excludes pelvic inflammatory disease
- Ovaries of typical size.
  - Ovarian tumors or cysts are unlikely.
- Uterus size.
  - Minimal enlargement consistent with early pregnancy may not be noted by an inexperienced examiner.
  - Endometrial polyps or submucosal leiomyomas (unusual in women <20 years) cannot be palpated by the examiner on the usual pelvic examination.
- Crampy lower abdominal pain.
  - Possible ectopic pregnancy
  - Incomplete or spontaneous abortion
    - History of 1 or 2 missed periods
    - Prior menstrual period lighter than normal
    - Tissue present in the vaginal canal or history of passing tissue
    - Other symptoms of pregnancy (eg, breast tenderness, nausea)
- Foul-smelling and bloody discharge.
  - Foreign body or retained tampon is likely.
  - Necrotic tumors can result in similar bleeding patterns.
- Pruritus or dysuria.
  - Vaginitis (*Trichomonas vaginalis*)
  - Cervicitis (*Neisseria gonorrhoeae* or *Chlamydia trachomatis* infection)

DIFFERENTIAL DIAGNOSIS

Prepubertal Girls

- Physiologic neonatal vaginal bleeding from falling estrogen levels
- Vulvovaginitis
  - With sexual abuse and gonococcal and chlamydial infection
  - Group A β-hemolytic streptococcus
  - With a history of preceding diarrhea, *Shigella* organisms

- Excoriations from pruritus
  - Irritants
  - Infection
  - Pinworm infestation
- Trauma
- Foreign body
- Sexual abuse
- Coagulopathy
- Hemangioma
- Condylomata
- Tumor

Pubertal Girls and Young Women

- Most teenagers who seek evaluation for genital bleeding in the first few years after menarche will have abnormal uterine bleeding (AUB), secondary to an immaturity of the hypothalamic-pituitary-ovarian (HPO) axis, with resultant anovulatory cycles.
  - AUB is considered a diagnosis of exclusion.
  - Disorders affecting the HPO axis can mimic AUB.
- Systemic disease.
  - Renal failure
  - Hepatic failure
  - Cancer
  - STI
- Conditions of the reproductive tract.
  - Vagina
    - Vaginitis
    - Trauma
    - Foreign body
    - Congenital anomaly (septum)
    - Neoplasia
  - Cervix
    - Cervicitis, erosion
    - Cervical polyp
    - Neoplasia
  - Uterus
    - Endometritis
    - Endometrial polyp
    - Submucosal leiomyoma
    - Arteriovenous malformation
    - Congenital anomaly
    - Neoplasia
  - Pelvis
    - Endometriosis
    - Pelvic inflammatory disease
- Pregnancy complications.
  - Spontaneous abortion
  - Ectopic pregnancy
  - Retained gestational products
  - Trophoblastic disease
- Endocrine disorders.
  - Hypothalamus, pituitary
    - Immature hypothalamic-pituitary-ovarian axis
    - Hyperprolactinemia
    - Anorexia nervosa, malnutrition
    - Excessive exercise
    - Emotional stress
    - Chronic illness
  - Adrenal
    - Congenital adrenal hyperplasia
    - Cushing disease
    - Adrenal insufficiency
    - Neoplasm
  - Thyroid
    - Hypothyroidism
    - Hyperthyroidism
  - Ovary
    - Polycystic ovary syndrome
    - Luteal phase abnormality
    - Premature ovarian failure
    - Neoplasia (hormone secreting)
- Hemostatic disorders.
  - von Willebrand disease
  - Coagulation factor deficiency
  - Platelet dysfunction (Glanzmann thrombasthenia, Bernard-Soulier syndrome)
  - Thrombocytopenia
    - Idiopathic thrombocytopenia
    - Immune thrombocytopenia
    - Bone marrow infiltration by malignancy (eg, leukemia)
    - Bone marrow failure disease (eg, aplastic anemia)
- Iatrogenic.
  - Hormonal medications
  - Anticoagulants
  - Neuroleptics
  - Intrauterine contraceptive device

LABORATORY EVALUATION

- For most cases of vaginal bleeding, relatively few laboratory tests are needed.
- Complete blood cell count with indices
  - Provides an objective measurement of the amount and duration of bleeding
  - Determines whether significant blood loss resulting in anemia has occurred
  - Guides the treatment approach for patients with an otherwise negative evaluation result
- Urinalysis.

- Urine pregnancy test.
  - Quantitative serum pregnancy test also should be obtained if ectopic pregnancy is suspected.
- Cultures in sexually active patients or where there is concern for sexual abuse.
  - *N gonorrhoeae*
  - *C trachomatis*
  - Trichomonas
  - Bacterial vaginosis
- Coagulation tests (prothrombin time, partial thromboplastin time, von Willebrand factor, platelet activation studies) if the patient has
  - Profuse hemorrhage
  - Menorrhagia at menarche
  - Family history of bleeding disorders
  - Unexplained heavy vaginal bleeding
- Measures of iron stores (eg, ferritin, reticulocyte count, hemoglobin content) may be useful.
  - Managing iron deficiency even in the absence of anemia
- If hormonal therapy is contemplated
  - Thyroid-stimulating hormone function tests
  - Prolactin
  - Luteinizing hormone and follicle-stimulating hormone
  - Coagulation tests
- Patients with any evidence of hyperandrogenism.
  - Free and total testosterone
  - Dehydroepiandrosterone sulfate

IMAGING

- Pelvic sonography when
  - Ectopic pregnancy is suspected.
  - The patient has a pelvic mass on bimanual examination.
  - Pelvic examination is difficult.

DIAGNOSTIC PROCEDURES

- Scotch tape slide test to look for pinworm eggs
- Endometrial biopsy: rarely indicated
- Dilation and curettage: rarely indicated
- Transvaginal ultrasonography: pelvic mass on bimanual examination

TREATMENT APPROACH

- Most cases of vaginal bleeding in adolescent girls are caused by anovulatory cycles.
  - In other instances, the physician must manage the bleeding without knowing the cause.
    - Treatment decisions can be guided using
      - The patient's clinical symptoms
      - Results of basic laboratory testing
- If treatment of the presumed cause does not end the bleeding, referral for a more thorough examination is indicated.

SPECIFIC TREATMENT

Neonates

- After birth, estrogen levels in the neonate decrease.
  - The result is a physiologic vaginal discharge that can be blood tinged or frankly bloody.
    - No treatment, except reassurance, is necessary.
    - The discharge usually disappears within 10 days.

Foreign Body or Vulvitis

- Removal of the foreign body.
  - Foreign bodies can often be washed out with a soft, flexible catheter.
  - Sharp objects should be removed carefully, under direct visualization.
  - Care should be taken to avoid causing pain by touching or manipulating the unestrogenized prepubertal hymen.
  - Referral to a gynecologist may be required if the patient is uncooperative.
- After removing a foreign body, bleeding should subside within 10 days.
  - If not, referral to a gynecologist is indicated.
    - The entire foreign body may not have been removed.
    - A tumor, not readily visualized by the primary care physician, may be the actual cause of the bleeding.
- Proper perineal hygiene.
  - Occasionally, systemic antibiotics may be necessary.

STIs

- Usually treated with antibiotics

Complications of Pregnancy

- Threatened or spontaneous abortion can be managed in the outpatient setting.
  - A physician experienced in the management of early pregnancy should be consulted.
  - For patients with bleeding disorders, consultation with a hematologist may be required.

AUB: Hormonal Therapy

- Indicated in
  - Teenagers who have moderate bleeding (enough to cause a decrease in hematocrit level to 11–12 g/dL).

- Girls who have menses every 1–3 weeks.
- The primary care physician may prefer the guidance of a more experienced physician.

- Combined oral contraceptives (COCs) or progestin alone
  - COCs are easier to use (1 pill is taken daily every day of the month).
  - If the patient has a condition in which COCs are contraindicated or this method is rejected by the patient or her parents
    - Medroxyprogesterone, 10 mg orally, can be given daily for 10–14 days.
    - Begin treatment on the first day of each month (calendar method) or on the 14th day of the menstrual cycle (day 1 being the first day of bleeding).
  - Assure the parents that
    - COCs are, in this instance, being used as treatment.
    - COCs are the most convenient way to package and deliver hormonal treatment.
    - Short-term use of COCs for 3–6 months is anticipated.
    - Close follow-up will be given during the treatment period.
  - Such an approach will often
    - Alleviate concerns about hormonal treatment.
    - Prevent rejection of these methods by the family.

AUB: Mild Bleeding

- No anemia.
  - Does not greatly upset the patient and her parents
    - Can be managed expectantly with no immediate, specific therapy
- Mild anemia.
  - Hemoglobin level 11–12 g/dL
  - Treated with iron supplementation
- Some problems will resolve in 3 or 4 cycles.
  - If the patient is sexually active, COCs can be prescribed to treat the bleeding as well as to provide contraception.
- Nonsteroidal anti-inflammatory drugs (NSAIDs).
  - Can also be used for their demonstrated antiprostaglandin effects.
    - Ibuprofen
    - Naproxen
  - Patients with von Willebrand disease or other hemostatic abnormalities may have increased bleeding with NSAIDs.

AUB: Severe Prolonged Heavy Bleeding

- Severe prolonged heavy bleeding accompanied by a decrease in hemoglobin level to ≤10 g/dL must be treated more aggressively.
  - An adolescent medicine or gynecologic consultation should be sought.
  - Clotting studies should be obtained.
  - Hospitalization should be strongly considered.
- COCs (1 tablet taken twice daily for 3–4 days) will generally stop the bleeding.
  - Lo Ovral every 4 hours may be necessary initially until the bleeding stops.
    - Then every 6 hours for 24 hours
    - Then every 8 hours for 4 days
    - Then twice daily to complete 3 weeks of hormonal therapy
  - Some physicians prefer to use conjugated estrogens (25 mg intravenously every 4 hours).
  - Antiemetic medications may be required to counteract the side effects of the high levels of estrogen contained in this regimen.
  - Withdrawal bleeding will occur 2–4 days after completion of this initial course of therapy.
  - Patients with significant bleeding should avoid the placebo pills contained in the COC pill packs and continue COCs until hemoglobin and hematocrit levels begin to normalize.
- Iron and folic acid supplementation.
  - Should be included as a part of the therapeutic plan
- Blood transfusion.
  - Need depends on the hemodynamic stability of the patient.
- Endometrial biopsy.
  - Rarely indicated
- Dilation and curettage.
  - Rarely indicated

WHEN TO REFER

- The patient is experiencing severe bleeding, or initial attempts to control the bleeding by the primary care physician have failed.
- Vaginal bleeding seems to be secondary to a chronic illness that the primary care physician cannot manage.
- The primary care physician feels uncomfortable performing a pelvic examination.
- Long-term hormonal therapy is required.
- Evidence exists for
  - Anatomic abnormality.
  - Complicated endocrine disorder.

- Coagulopathy, or additional guidance is required for further evaluation of a coagulation or hemostatic disorder.
- Malignancy.
- Sexual abuse.

WHEN TO ADMIT

- Severe prolonged heavy bleeding accompanied by a decrease in hemoglobin level to ≤10 g/dL
- Hemodynamic instability

FOLLOW-UP

- All patients with abnormal vaginal bleeding should be instructed to maintain a menstrual calendar to facilitate follow-up management.
- Patients with mild bleeding should be reevaluated in 6–8 weeks.
- Patients with severe bleeding require long-term, close follow-up.
- Even when measures succeed in controlling the vaginal bleeding, an appreciable number of patients will continue to have menstrual abnormalities.

COMPLICATIONS

- Anemia

DEFINITION

- *Vaginal discharge* is fluid produced by glands in the vaginal wall and cervix that drains from the opening of the vagina.
  - Not necessarily abnormal
  - May represent the vagina's response to changing estrogen levels

HISTORY

- Prepubertal girls
  - Inquire about hygiene.
    - Wiping from the anus toward the vagina brings intestinal flora to the vaginal introitus.
    - Use of chemicals, such as bubble baths, deodorants, or strong laundry detergents, can irritate the vulva and vagina.
  - Parents should be asked about recent or concomitant illness.
    - *Streptococcus pyogenes* infection (with or without scarlet fever).
    - *Shigella flexneri* infection, occurring coincident with or after an episode of diarrhea.
    - Systemic illnesses, such as varicella.
    - Rectal infestations with *Enterobius vermicularis* (pinworms) can lead to vaginitis if the eggs are deposited around or in the vagina.
    - *Candida vulvovaginitis* is an uncommon cause of vaginal discharge or vulvovaginitis in prepubertal girls unless the child
      - Has recently taken antibiotics
      - Has diabetes mellitus
      - Is still in diapers
      - Is immunocompromised
  - Sexual abuse should be considered in any child with vaginal discharge.
- Pubertal and postpubertal adolescents
  - In addition to previously listed, inquire about sexual activity.
    - Many teenagers fear admitting to sexual intercourse.
      - Negative response to queries about sexual activity should not rule out consideration of a sexually transmitted organism as the cause.
  - Presence of a foreign body (eg, a retained tampon, condom).
  - Use of spermicides or douching can cause vaginitis.

PHYSICAL EXAMINATION

- Prepubertal girls
  - Physical examination should include
    - Entire genital and anal area
    - Vulva, urethral meatus, and vaginal introitus
  - Care must be taken to avoid touching or manipulating the sensitive unestrogenized hymen on a prepubertal child to minimize pain.
  - Infections in prepubertal girls usually involve the vulva as opposed to only the vagina.
  - Presence of bruises, lacerations, or scrapes in the genital area is suggestive of sexual abuse.
    - In most cases of child sexual abuse, examination reveals no evidence of trauma.
  - Excoriations around anus or vagina suggest itching caused by pinworms.
  - A rash that spares skinfolds is consistent with an irritative cause.
  - A rash that is predominantly within the skinfolds suggests candidiasis.
  - Positioning options for examination.
    - Sitting on the mother's lap with legs spread so they dangle outside mother's legs
    - Lying supine in the frog-leg position
    - Lying face down in the knee-chest position
  - If a foreign body is thought to be present but not visualized
    - Irrigating the vagina with a soft, flexible catheter and tepid saline solution will often flush out bits of toilet paper or small objects.

DIFFERENTIAL DIAGNOSIS

- Causes of vaginal discharge in prepubertal girls
  - Nonspecific vaginitis (the most common cause)
  - Irritative agents (bubble baths, sand)
    - The vulva is often involved as well.
    - Nonabsorbent occlusive clothing (eg, nylon undergarments, tights, bathing suits) also irritate the vulva, leading to skin breakdown and infection.
  - Poor perineal hygiene
  - Foreign body
  - Associated systemic illness (eg, group A streptococci, varicella)
  - Other respiratory pathogens (eg, *Haemophilus influenzae*)
  - Enteric infections
    - *Escherichia coli* with foreign body
    - *Shigella* organisms
    - *Yersinia* organisms
    - *E vermicularis* (pinworm)

- Sexually transmitted infections (strong presumption of sexual abuse in prepubertal girls)
  - *Neisseria gonorrhoeae*
  - *Trichomonas vaginalis*
  - *Chlamydia trachomatis* (Whether this organism alone can cause discharge is unclear. *C trachomatis* is often isolated in conjunction with *N gonorrhoeae*.)
- Primary vulvar skin disease
- Tumor, polyps (rare)

■ Major causes of vaginal discharge in pubertal girls

- *Candida albicans*
  - Discharge: thick, white, curd-like, cheesy
  - Odor: none usually
  - pH: 4.5 (obtained from mid-vagina with nitrazine paper)
  - Dysuria: frequent
  - Pruritus: 4+
  - Other clues
    - Vulva affected
    - Associated with use of some oral contraceptives and, in some women, antibiotic use
- *T vaginalis*
  - Discharge: frothy; yellow-green or gray
  - Odor: foul-smelling
  - pH: 5.2–5.5
  - Dysuria: frequent
  - Pruritus: yes
  - Other clues
    - Lower abdominal pain
    - Strawberry cervix (colpitis macularis) (punctate hemorrhages)
- Bacterial vaginosis
  - 3 of the following signs or symptoms for diagnosis:
    - Discharge: homogeneous, thin, white discharge that smoothly coats the vaginal walls
    - Odor: a fishy odor to the vaginal discharge before or after addition of 10% potassium hydroxide (ie, the whiff test)
    - pH: >4.5
    - Clue cells on microscopic examination
  - Dysuria: no
  - Pruritus: slight
  - Other clues
    - Occurs in association with anaerobes and *Gardnerella vaginalis*
- Herpesvirus (occasionally associated with vaginal discharge)
  - Pain or a burning sensation is felt in the genital area.
  - Vulva is reddened.
    - Groups of small vesicles are noted on the vulva, in the vagina, or on the cervix.
    - If the vesicles have ruptured, only small ulcerations may be present.
  - Inguinal adenopathy, fever, and malaise are usually present if this attack is the first one.

LABORATORY EVALUATION

■ Slide preparation.

- If sufficient vaginal discharge is present, several drops of the secretion should be placed on 2 glass slides.
- If discharge is scant, a saline-moistened cotton swab can be introduced into the vagina to obtain samples.
- First slide.
  - Add several drops of physiologic (normal) saline solution.
- Second slide.
  - Add several drops of 10% potassium hydroxide and gently heat to dissolve epithelial cells, allowing visualization of hyphae.

■ Culture.

- Culture is the most sensitive and specific commercially available method of diagnosis for *T vaginalis.*
- If indicated, culture for *N gonorrhoeae* and *C trachomatis.*
  - Alternatively, nucleic acid amplification is easier to perform and more sensitive.

■ Cellophane tape with its sticky side applied to the perianal area and then onto a glass slide may reveal the typical eggs of *E vermicularis.*

■ Less common but useful tests for bacterial vaginosis include

- Gram stain: Centers for Disease Control and Prevention (CDC) gold standard
- DNA probe-based test
- Card test to detect increased pH, trimethylamine, and proline-aminopeptidase

■ Typical findings include

- *C albicans:* hyphae on potassium hydroxide examination
- *T vaginalis:* motile trichomonads on wet preparation (Avoid drying specimen.)

- Bacterial vaginosis: clue cells on wet preparation (bacteria-coated epithelial cells)

TREATMENT APPROACH

- In the newborn, no treatment is needed, and the discharge usually resolves by 10 days of age.
- Prepubertal girls.
  - If the history or physical examination suggests an irritative origin
    - Discontinue the offending agent.
    - Have the child wear cotton underpants.
    - Sitz baths will provide temporary relief until natural healing takes place.
  - Removal of a foreign body will result in rapid improvement and cessation of the discharge.
  - Pinworm infestations should be treated in the usual manner (mebendazole, pyrantel pamoate, or albendazole).
  - Infections caused by poor personal hygiene will respond to general measures, coupled with instructions about proper perineal hygiene.
  - If discharge is associated with another infection (eg, *S pyogenes, Shigella* organisms), treat the underlying infection.
  - When the organism causing the vaginal discharge is found to be sexually transmitted, more comprehensive evaluation and treatment are required.
    - A report to child protective services should be made.
- Pubertal and postpubertal adolescents.
  - Persistent discharge unresponsive to therapy may indicate
    - Noncompliance with treatment
    - Reinfection by an untreated sexual partner
  - For sexually transmitted infections
    - Consult current CDC recommendations for specific antimicrobial regimen.
    - Sexual partner(s) must be notified and treated.
    - Patients should refrain from sexual intercourse until treatment is completed.
  - In the absence of *N gonorrhoeae, C trachomatis*, and *T vaginalis,* or causes described previously, recommend
    - Trial of sitz baths
    - Use of cotton as opposed to nylon underwear
    - Careful attention to perineal hygiene
- Candidal infections can be especially difficult to treat and may recur.
  - Predisposing factors include
    - Oral contraceptive use
    - Broad-spectrum antibiotic use
    - Diabetes mellitus

SPECIFIC TREATMENT

Prepubertal Girls

- Nonspecific vaginitis
  - Usually responds to thorough perineal hygiene, sitz baths, and mild soaps.
  - Patients should
    - Wear white cotton underpants and loose-fitting pants or skirts.
    - Avoid nylon tights and tight pants.
    - Avoid sitting for long periods in nylon bathing suits.
    - Wipe only from front to back.
  - For persistent cases, treat in standard childhood doses for 10–14 days with
    - Amoxicillin
    - Amoxicillin-clavulanate
    - Cephalosporin
    - Clindamycin
  - Alternatively, a 1- to 2-month daily low-dose antibiotic may be helpful.
  - If unsuccessful, antibiotic or estrogen creams may be used.
    - Mupirocin
    - Gentamicin
    - Metronidazole
    - Clindamycin

Pubertal and Postpubertal Adolescents

- Vulvovaginal candidiasis (*C albicans*)
  - Topical therapy for 7–14 days *or*
  - Oral fluconazole, 150 mg, repeated 72 hours after the first dose.
  - If more intensive treatment is warranted
    - Oral fluconazole, 150 mg once weekly for 6 months after initial treatment of 1 dose every 3 days for 3 doses
  - A variety of month-long antifungal treatments have been successful; however, intravaginal treatment over a long period is inconvenient.
  - Long-term ketoconazole has been used to suppress recurrent infection, but hepatotoxicity is a concern.
  - Male sexual partners should be treated if they have any signs or symptoms of penile candidal involvement.

- *T vaginalis*
  - Metronidazole 2 g orally in a single dose.
    - Alternatively, this medication can be given as 500 mg twice daily for 7 days.
    - Some strains of *T vaginalis* have decreased susceptibility to metronidazole.
    - Repeated failures should be treated with 2 g once daily for 3–5 days.
    - The patient should be told to avoid alcohol until 24 hours after completion of therapy.
  - Sexual partners must be treated.
- Bacterial vaginosis
  - Metronidazole 500 mg orally twice daily for 7 days *or*
  - Metronidazole gel 0.75% one full applicator (5 g) intravaginally once daily for 5 days *or*
  - Clindamycin cream 2%, one full applicator (5 g) intravaginally every night at bedtime for 7 days *or*
  - Alternative regimens that include
    - Metronidazole 2 g orally in a single dose
    - Clindamycin 300 mg orally twice daily for 7 days
    - Clindamycin ovules 100 g intravaginally every night at bedtime for 3 days

WHEN TO REFER

- If the physician is uncomfortable with evaluating genital symptoms in prepubertal girls
- If the physician lacks experience in performing pelvic examinations
- If the evaluation yields evidence of sexual abuse
- If discharge persists despite seemingly appropriate therapy

PREVENTION

- Proper perineal hygiene
  - Keeping the area clean
  - Wiping from front to back
- Patients should be advised that the child should
  - Wear white cotton underpants and loose-fitting pants or skirts.
  - Avoid nylon tights and tight pants.
  - Avoid sitting for long periods in nylon bathing suits.

DEFINITION

- *Verrucae* (warts) are virally induced tumors of the skin.

SIGNS AND SYMPTOMS

- Clinical appearance of warts varies, depending on the type and location.
- Common wart, or verruca vulgaris.
  - Easily recognized as a superficial, light-colored papule
  - Coarse, roughened surface
- Warts are often studded with black specks.
  - Actually small, superficial dermal capillaries
- Warts are sometimes found in a linear array, presumably as a result of autoinoculation through scratching.
- Not all warts appear as verrucous papules.
  - Variants include
    - Flat (planar) warts
    - Plantar warts
    - Periungual warts
    - Anogenital warts

DIFFERENTIAL DIAGNOSIS

- The distinctive clinical appearance of the common wart usually presents no problem in diagnosis.
- Epidermal nevi.
  - Hamartomas that may be confused with warts
  - They are
    - Softer
    - More pigmented
    - More persistent
    - Much less common
- Flat (planar) warts appear as small, flesh-colored papules.
  - Flat warts have sharp borders and a finely verrucous surface.
  - When located on the face, warts may be confused with the closed comedones (whiteheads) seen in acne.
    - On close inspection, however, flat warts are seen to have sharp borders and a finely verrucous surface.
    - Closed comedones are smooth, dome-shaped lesions.
- Plantar warts.
  - Named for their appearance on the plantar surface of the foot.
  - Often confused with calluses and corns.
    - Corns are much less common in children.
  - Large plantar warts are often composed of confluent smaller warts.
    - Form a mosaic wart surrounded by satellite lesions.
  - Differ from corns by having a verrucous surface that interrupts skin markings and often punctuated with black specks.
    - In some cases, the 2 entities can only be distinguished by paring down the surface.
      - Wart tissue still has a roughened texture and remains the same size as it is pared.
      - Corn tissue is smooth, and it becomes smaller in diameter as it is pared.
- Periungual warts.
  - Occur around the nail fold and should not pose diagnostic difficulty
  - Warts under free edge of the nail
    - Can cause nail plate to separate from nail bed.
    - May be confused with fungal infection.
    - On close inspection, the verrucous nature of the wart usually can be appreciated.
- Anogenital warts (condylomata acuminata).
  - Sometimes, but not always, acquired by sexual contact
  - Can usually be identified as verrucous papules
  - Sometimes small or flat and more difficult to see
  - May be confused with the less common condylomata lata found in secondary syphilis
    - Condylomata acuminata is drier and more verrucous.
    - Condylomata lata is flat and moist.
    - If doubt exists, a serologic test for syphilis should settle the issue.

DIAGNOSTIC APPROACH

- Warts are almost always diagnosed clinically.
- If doubt exists, skin biopsy can provide histologic confirmation.

DIAGNOSTIC PROCEDURES

- Anogenital warts: acetowhitening technique can aid in the diagnosis.
  - A compress containing 5% acetic acid is applied for several minutes to the suspected lesion.
  - Reexamine, ideally under magnification.
  - With this technique, warty tissue turns white and is visualized more easily.

TREATMENT APPROACH

- Among schoolchildren.
  - Warts are often a focus for teasing and insensitive remarks.
  - Children usually ask that their warts be treated because of social pressure.
  - Successful therapy gives patients the opportunity to feel better about themselves and their appearance.
- Warts commonly regress spontaneously.
  - Time required varies considerably.
  - In some patients, therapy may only serve to appease the patient while nature takes its course.
- In some patients, the destructive techniques may
  - Initiate an inflammatory reaction.
  - Expose the viral antigen to the body's immune system, which rejects the wart.
- Whenever warts are treated, the physician must guard against doing harm by being overzealous.
  - Surgical excision is usually discouraged.
  - Radiotherapy is contraindicated.
- The goal of therapy is to shorten the time required for the wart to disappear.

SPECIFIC TREATMENTS

Cryotherapy

- Tissue is frozen by applying liquid nitrogen (-195°C [-319°F]).
  - Swab
  - Canister delivery system
- Freezing should extend beyond wart to include a 1- to 2-mm rim of normal skin.
- To destroy affected tissue more effectively, the wart may be refrozen after initial thaw.
- Patients must be advised that
  - The frozen area will be sore for several days.
  - A blister may form.
  - Several weeks are usually needed for the wart to turn dark and drop off.
- Cryotherapy is a favorite office therapy for common warts.
- For small warts, a single treatment is often successful.
- Large warts frequently need to be refrozen about every 3 weeks.
- Scars may result but are uncommon.
- Skin may become hypopigmented.
- Freezing warts on the fingers.
  - Care must be taken to avoid freezing too deeply.
  - Underlying structures, such as digital nerves, can be damaged.
- Over-the-counter freezing treatments.
  - May not be as effective as liquid nitrogen

Keratolytic (Acid) Therapy

- Slower and involves more patient participation than freezing.
  - Less immediately painful
  - Least likely to cause scarring
- Variety of acids are available for treating warts.
  - Salicylic acid is available as a solution in 26% (Durasal) and 27.5% (Virasal) concentrations.
- Convenient outpatient medication incorporates 17% salicylic acid in a polyacrylic or flexible collodion vehicle (Occlusal-HP, Duofilm).
  - Dries rapidly to prevent spread of acid onto surrounding skin.
  - Patients are instructed to
    - Apply medication at bedtime.
    - Cover area with thick tape.
  - Superficial necrotic tissue should be pared daily using a pumice stone.
- Thick palmar or plantar warts often require stronger acid, such as a 40% salicylic acid plaster.
  - These products can be bought over the counter (Mediplast and Duofilm patches).
  - Patients need instruction in application.
  - A plaster is cut to match size of the wart.
  - The adhesive, medicated side is applied to the wart and held in place with tape.
  - The plaster is changed every 24 hours and the macerated wart pared daily using a callus grater.
- Flat warts are often treated successfully by
  - Nightly applications to the affected area with
    - Topical adapalene (Differin)
    - Tretinoin (Retin-A)
    - Imiquimod (Aldara)
  - Products act as peeling agents.
  - Painful irritation may necessitate less frequent use.
- Home acid therapies usually require ≥1 month of continuous use to be effective.
  - If no progress has been made after several months, other treatments should be considered.
  - For deeply seeded warts, paring after a combination of acid and cryotherapy usually provides successful treatment.
- Caustic acids, such as trichloroacetic acid at concentrations of 30%–100%, are reserved for office treatment of palmar or plantar warts.
  - Must be carefully applied
  - Can cause destruction of normal tissue

- Cantharidin is a protein phosphatase inhibitor produced by the Spanish fly, *Lytta vesicatoria*.
  - Penetrates the epidermis.
  - Causes acantholysis.
  - Results in vesiculation.
  - Destroys infected keratinocytes.
  - Can be used for almost all nongenital warts.
  - Reapplication may be required at 1- to 3-week intervals.
  - Painless when initially applied.
  - Causes little risk of scarring.
  - Occasionally, a ring wart will develop at the edge of the treated site.
- All of these treatments are nonspecific.
- In some instances, different modalities are used in sequence.

Immunotherapy

- Imiquimod cream (in 5% [Aldara] or 3.75% [Zyclara] concentrations)
  - Immunomodulator that augments cellular immunity by inducing a variety of cytokines.
  - Can be self-administered daily or every other day.
  - Should be left on overnight.
  - Controlled, multicenter trials have evaluated its role in treating genital warts.
  - Smaller studies and case reports are suggesting its potential as an alternative treatment.
    - Used alone or in combination with other modalities, such as cryotherapy and salicylic acid
  - Mechanism of action may make imiquimod especially useful in treating nongenital warts in immunosuppressed patients.
- Sensitization to squaric acid
  - Therapeutic option available as dibutyl ester in acetone in concentrations of 0.5% and 1% for home use and 2% for office use.
    - Absolutely contraindicated in patients with vitiligo because it can exacerbate the associated depigmentation.
  - Solution is first applied in the office to a small area (usually the inner arm), usually causing no reaction, or occasional mild cotton-tipped applicator to the lesions.
    - Applied 3 times per week.
    - Gradually increased by one night a week on a weekly basis as tolerated.
    - Usually improvement is seen by 3 weeks and clearance by 7 weeks.
    - Complete clearance rates range from 58% (home use) to 68% (in-office use) to 86.2% (in-office application after 70% salicylic acid in petrolatum used at home before therapy).
- Intralesional therapy involving sensitization to antigens
  - *Candida,* mumps, or *Trichophyton.*
  - Used by dermatologists when topical therapies fail.
  - Response rates range from 54%–87% in treated warts and 34%–78% in untreated, distant warts.
- Zinc
  - Can function as an immunomodulator, and its deficiency causes lymphopenia.
  - 2 studies in zinc-deficient patients with warts suggest that oral zinc sulfate may be an effective, inexpensive, and painless therapeutic alternative.
  - Additional controlled studies in non-deficient patients are needed to confirm its therapeutic efficacy.

Electrodesiccation and Laser Therapy

- Electrodesiccation can be preceded or followed by curettage.
  - The advantage is the patient leaves the office without visible evidence of the wart.
  - Cure rate is probably no higher than with cryotherapy.
  - Disadvantages include
    - The procedure requires local anesthesia.
    - Scarring is more likely.
- Carbon dioxide laser can be used to destroy large or refractory warts.
  - Risk of scarring is significant.
- Pulsed dye laser destroys vascular component of the wart.
  - May become another alternative
  - Less risk of scarring
- Used for some recalcitrant warts, particularly
  - Palmar
  - Plantar
  - Periungual
  - Anogenital

Other Treatments

- A recent study showed that duct tape occlusion therapy was significantly more effective than cryotherapy in treating nongenital warts.
- Efficacy of oral cimetidine in the treatment of warts is still controversial.
  - May be useful in the treatment of flat warts.
  - Use in other types of warts is under investigation.

- Phototherapy.
  - Uses topical photosensitizing agents, most commonly 5-aminolevulinic acid, followed by exposure to light.
  - Accumulated porphyrins to unleash a photo-oxidation cascade that destroys treated cells.
  - In randomized controlled trials for recalcitrant palmar and plantar warts, cure rates ranged from 56%–75%, with 94.4% clearance of facial warts in one study.

Treatment of Genital Warts

- Condylomata in children are usually asymptomatic.
  - May be treated to
    - — Curtail spread.
    - — Allay parental concerns.
  - Some forms of therapy may be painful.
  - Recurrence rates may be ≤50%.
  - Weighing the risks versus benefits is wise before treating genital warts in children.
- 2 therapeutic options for condyloma have been approved by the US Food and Drug Administration (FDA) in adults; case reports with children have shown promise.
  - Imiquimod
  - Podophyllotoxin
- Podophyllin.
  - Available in 10%–25% solutions in alcohol or benzoin
  - Exclusively for office use
  - Painless when applied
  - Can be toxic if used over large areas
  - Must be washed off within 6–8 hours of application
  - Marketed as purified 0.5% podophyllotoxin (Condylox) solution or gel
  - Can be very irritating for some patients
- Sinecatechins
  - Partially purified fraction of the water extract of green tea leaves from *Camellia sinensis* (L.) O Kuntze; mixture of catechins and other green tea components
    - — Thought to have antioxidant, antiviral, and anti-tumor activity against warts.
  - Approved by the FDA for adults
    - — Use in children has not yet been reported in the literature.
  - Marketed as an ointment (Veregen) to be applied 3 times a day for ≤16 weeks
- Other options include
  - Cryotherapy
  - Lasers
  - Caustic acids
  - Cimetidine

WHEN TO REFER

- Patients with persistent warts may benefit from evaluation by a dermatologist.

COMPLICATIONS

- Major complications are those caused by over-zealous therapy, resulting in
  - Short-term discomfort
  - Scarring
- The annoyance of a wart (usually temporary) must be balanced against the inconvenience of a scar.
  - Lifelong
  - May be unsightly
  - Sometimes tender, particularly if present on a pressure-bearing surface

PROGNOSIS

- Most warts eventually involute spontaneously.
  - Probably through immunologic rejection
- The time required for involution varies greatly.
  - Predicting resolution for an individual patient is impossible.
- The therapies discussed in the Specific Treatments section result in clearing in most cases.

PREVENTION

- Gardasil
  - FDA-approved vaccine.
    - — For use in female patients 9–26 years of age for human papillomavirus (HPV) types 6, 11, 16, and 18, which cause 70% of genital warts
    - — Also approved for male patients 9–26 years of age to prevent genital warts from HPV types 6 and 11.
  - Administered 3 times over a 6-month period.

DEFINITION

- Vitamin D insufficiency
  - Defined by the American Academy of Pediatrics as serum 25(OH)D <20 ng/mL (50 nmol/L)
- Vitamin D deficiency
  - Defined by the National Academies of Sciences, Engineering, and Medicine, Health and Medicine Division (HMD), as serum 25(OH)D <12 ng/mL (30 nmol/L) associated with rickets
- Indicators of overt disease
  - Rickets and osteomalacia
    - Seen as serum 25(OH)D levels <10–12 ng/mL (25–30 nmol/L)

HISTORY

- At birth
  - Intrauterine growth restriction
  - Hypocalcemia
  - Congenital rickets
  - Neonatal seizures resulting from hypocalcemia
- Early infancy
  - Hypocalcemia
    - The typical nonskeletal presentation in early infancy
  - Hypocalcemic seizures or tetany
  - Craniotabes
- Late infancy and childhood
  - Delayed physical growth (short stature)
  - Delayed gross motor development
  - Inability to bear weight on legs or walk
  - Waddling gait
  - Muscle weakness
  - Frontal bossing
  - Delayed closure of fontanel
  - Swelling of wrists, ankles, or knees
  - Rachitic rosary (enlargement of costochondral junctions)
  - Bowing of lower legs
  - Pigeon chest deformity
  - Rarely: stridor, cardiomyopathy, and fracture
  - Increased risk of acute lower respiratory tract infection
- Seizures and tetany
  - Typically in association with hypocalcemia
  - Reported in periods of increased growth velocity (eg, early infancy, adolescence)
- With rapid growth
  - Increased demand for calcium cannot be met in a timely fashion.
  - Patient may present with hypocalcemia even before bone demineralization or rickets secondary to profound vitamin D deficiency is observed.
- In later infancy and early childhood, the most common presentations are
  - Skeletal abnormalities
  - Delayed motor development
  - Suboptimal physical growth
  - Muscle weakness and myalgias
- Maternal vitamin D deficiency
  - More common in mothers of infants with rickets
  - Should prompt suspicion of subclinical vitamin D deficiency in the infant
- Threshold for diagnosing vitamin D deficiency should be low
  - In winter months
  - In children at high risk, including
    - Those with rapid growth
    - Dark-skinned, breastfed infants without vitamin D supplementation
    - Children on chronic anticonvulsant therapy
    - Children with chronic disorders associated with malabsorption (eg, cystic fibrosis, inflammatory bowel disease)

PHYSICAL EXAMINATION

- Skeletal abnormalities
  - Widening of the wrists and the ankles
  - Bowlegs (genu varum)
  - Abnormal gait
  - Prominence of costochondral junctions (rachitic rosary)
  - Skull abnormalities (eg, delayed closure of fontanels, craniotabes, and frontal bossing)
- Poor growth
  - Length for age <5th percentile
  - Weight for age <5th percentile
- Delayed motor development
- Hypocalcemic seizures
- Rarely, dilated cardiomyopathy with heart failure, associated with hypocalcemia

DIFFERENTIAL DIAGNOSIS

- Childhood rickets also can be caused by
  - Phosphate deficiency caused by abnormal phosphate metabolism
  - Calcium deficiency
  - 1α-hydroxylation defect (vitamin D–dependent rickets, type 1)
  - Impaired biological response to 1,25-dihydroxy vitamin D (vitamin D–resistant rickets)
  - Renal tubular acidosis
  - Renal osteodystrophy

LABORATORY EVALUATION

- Common laboratory findings in vitamin D–deficiency rickets include
  - Hypophosphatemia
  - Varying degrees of hypocalcemia
  - Elevated serum alkaline phosphatase (ALP) and parathyroid hormone levels
- Other biochemical abnormalities include
  - Generalized aminoaciduria
  - Reduced urinary calcium excretion
- The diagnosis of vitamin D–deficiency rickets is confirmed by measuring serum 25(OH)D concentration.
  - No absolute threshold level.
  - Serum 25(OH)D level is usually <20 ng/mL (50 nmol/L).
  - Values <12 ng/mL (30 nmol/L) are very common.
  - Measurement of serum 25(OH)D levels is also indicated when a child presents with clinical manifestations of rickets.
- In cases of unexplained fractures in children, to rule out organic causes as the etiology of the fracture(s), it is imperative to check levels of
  - Serum calcium
  - Phosphorus
  - ALP
  - 25(OH)D

IMAGING

- Radiologic features include
  - Irregular bone mineralization
  - Cortical thinning of long bones
  - Metaphyseal widening
  - Fraying and cupping
  - Underdevelopment of the epiphysis

TREATMENT APPROACH

- Vitamin D and calcium therapy.
  - For infants and children who
    - Manifest clinical features of hypocalcemia as a result of vitamin D deficiency *or*
    - Present with rickets and have serum 25(OH)D levels that are in the deficient range.
  - In active rickets, vitamin D supplementation in a total cumulative dose of 200,000–600,000 IU.
  - 3 different dosing regimens have been advocated.
    - Daily oral administration of 2,000–5,000 IU vitamin D for 2–3 months to normalize the 25(OH)D levels and replenish vitamin D stores
    - Weekly 50,000 IU vitamin D for 8 weeks or until the serum 25(OH)D level is normalized
    - Single or divided dose of 200,000–400,000 IU vitamin D (Stoss therapy) if lack of compliance is a concern. (Close monitoring for hypercalcemia is required.)
- Monitoring and maintenance.
  - Serum calcium, phosphorus, and ALP should be monitored in the first month.
  - Serum 25(OH)D levels should be monitored during the first 3 months and at 3-month intervals with calcium, phosphorus, and ALP to achieve a reference calcium level and serum 25(OH)D >20 ng/mL (50 nmol/L).
  - After the serum calcium and vitamin D levels have returned to reference range, vitamin D intake will be reduced to a minimum of 400 IU daily as a maintenance dose with adequate calcium intake.
- Symptomatic hypocalcemia should be treated with calcium supplements.
  - 10% calcium gluconate solution at 10–20 mg of elemental calcium per kilogram intravenously slowly over 5–10 minutes.
  - Repeated doses may be necessary.
  - Oral calcium supplements should be continued until serum calcium levels return to reference range.

SPECIFIC TREATMENT

- As part of a multivitamin preparation (typically 400 IU/mL) *or*
- Vitamin D–only preparations
- Upper limits of safety for vitamin D supplementation are
  - For infants ≤6 months: 1,000 IU/d
  - Infants 6–12 months: 1,500 IU/d
  - Toddlers 1–3 years: 2,500 IU/d
  - Children 4–8 years: 3,000 IU/d
  - All patients >8 years: 4,000 IU/d
- The main concern when dosing any vitamin or medication is correct dispensing.

FOLLOW-UP

- A biochemical monitoring plan during treatment of vitamin D–deficiency rickets includes
  - At 1 month: serum calcium, phosphorus, ALP
  - At 3 months: serum calcium, phosphorus, ALP, and 25(OH)D
  - At 6 months and again at 1 year: serum 25(OH)D levels

- Radiologic evaluation should be repeated at 3 months and after 1 year to monitor.
  - Skeletal abnormalities usually take much longer than biochemical abnormalities to return to reference range.

PREVENTION

- Vitamin D supplementation
  - For infants at high risk of vitamin D insufficiency, especially
    - Breastfed or formula-fed infants whose vitamin D intake is <400 IU daily
- Minimum of 400 IU of vitamin D intake daily for infants and children through
  - Vitamin D supplements
  - Food fortification
    - Recent HMD report suggests a 600 IU recommended daily allowance.
- Higher doses of vitamin D supplements may be required in other high-risk infants, including
  - Infants with fat malabsorption
  - Infants on anticonvulsant medications

Vomiting

DEFINITION

- Vomiting is a common symptom of acute and chronic illness in childhood.
- Vomiting is an active process requiring coordination between the autonomic and somatic nervous systems, usually preceded by nausea in association with increased salivation and diaphoresis.
- Vomiting should be distinguished from regurgitation, a passive reflux of gastric contents into the esophagus and mouth through a relaxed lower esophageal sphincter.
  - In infancy, regurgitation, or spitting up, is very common.
    - Most often a developmental event
    - Has no sequelae and gradually resolves
  - *Pathologic gastroesophageal reflux* (GER) is defined by the association of regurgitation with severe complications, including
    - Esophagitis with or without anemia secondary to blood loss or stricture
    - Recurrent apnea
    - Aspiration pneumonia
    - Failure to thrive

HISTORY

- Bilious vomiting usually occurs only with ileus or intestinal tract obstruction below the ampulla of Vater in the second portion of the duodenum.
  - Especially when associated with the first vomitus.
  - In newborns, bilious vomiting can be associated with necrotizing enterocolitis, especially with blood in the stool.
  - In older children who vomit persistently, reflux of bile from the duodenum into the stomach may lead to bilious vomiting without gastrointestinal (GI) tract obstruction.
  - When a previously well newborn develops sudden onset of bilious vomiting, especially within the first few days of life
    - Consider a malrotation with secondary midgut volvulus, a surgical emergency requiring early diagnosis and surgical intervention.
- Projectile vomiting commonly occurs with pyloric stenosis.
  - When this condition persists, gastric atony may eliminate the projectile character.
  - Vomiting associated with increased intracranial pressure may be projectile and may take place in the absence of nausea or retching.
- Persistent vomiting in a newborn or young infant who has no evidence of infection usually suggests
  - Congenital GI anomaly.
  - Inborn error of metabolism.
  - Central nervous system (CNS) abnormality, eg, hydrocephalus, subdural effusion.
  - If history and physical examination do not suggest a cause, evaluating all 3 possibilities simultaneously is best.
  - Beyond the first week of life but within the first 2 months, pyloric stenosis is the most common cause of persistent vomiting.
  - Persistent or recurrent vomiting without other symptoms may be the major manifestation of an emotional disorder.
  - A complete psychosocial history is an important part of the evaluation.
- When an older child exhibits acute vomiting and somnolence, the clinician should always consider
  - Drug overdose, especially acetaminophen, aspirin, or iron
  - Meningoencephalitis
  - Inborn errors of mitochondrial fatty acid oxidation
- Cyclic vomiting is characterized by repeated episodes of vomiting.
  - At least 3 attacks over a 6-month period or 5 attacks in any interval.
  - Episodes last 1 hour–10 days and are separated by at least 1 week.
  - Episodes are stereotypic.
  - Sometimes associated with abdominal pain.
  - Uncontrollable vomiting and retching are typical.
  - Patients are well between episodes.
  - ~10% of these children have an identifiable disorder as the probable cause.
    - GI.
    - Extraintestinal (renal, metabolic, neurologic).
    - Abdominal migraine is a common cause of cyclic vomiting.
      - Paroxysmal onset of repetitious attacks is often relieved with sleep.
      - Strong family history of migraine.
      - May be accompanied by typical migraine headache.
    - Abdominal epilepsy is a much less common cause of cyclic vomiting.

PHYSICAL EXAMINATION

- Acute abdominal signs, such as generalized tenderness and rigidity, suggest surgical abdomen.
- Observe the shape of the abdomen.
  - Distention may be associated with an obstruction, paralytic ileus, ascites, or an abdominal mass.
- A succussion splash (the splashing sound present when a patient who has fluid in a hollow organ is shaken) may be present with gastric outlet obstruction.

DIFFERENTIAL DIAGNOSIS

Causes of Emesis, by Usual Age of Earliest Occurrence

- Infancy/early childhood
  - GI
    - Congenital
      - Regurgitation—GER (developmental or pathologic)
      - Atresia—stenosis (tracheoesophageal fistula, antral web, intestinal atresia, annular pancreas)
      - Duplication
      - Volvulus (secondary to an error in rotation and fixation or to Meckel diverticulum)
      - Congenital bands
      - Meconium ileus (cystic fibrosis), meconium plug
      - Hirschsprung disease (congenital megacolon)
    - Acquired
      - Neonatal necrotizing enterocolitis.
      - Pyloric stenosis.
      - Cow milk protein allergy.
      - Acute infectious gastroenteritis.
      - Postviral gastroparesis.[1]
      - Food allergy.
      - Eosinophilic esophagitis.
      - Intussusception.
      - Celiac disease—risk is inherited, but clinical manifestations occur only after introduction of gluten in diet.
      - Incarcerated hernia—inguinal, internal secondary to old adhesions.
      - Adynamic ileus—the mediator for many non-GI causes of vomiting.
      - Chronic granulomatous disease with gastric outlet obstruction.
  - Non-GI
    - Infectious
      - Otitis
      - Urinary tract infection
      - Pneumonia
      - Upper respiratory tract infection
      - Sepsis
      - Meningitis
    - Metabolic
      - Aminoaciduria and organic aciduria
      - Galactosemia
      - Fructosemia
      - Adrenogenital syndrome
      - Renal tubular acidosis
      - Hyperammonemia
      - Disorders of fatty acid oxidation (eg, medium-chain acyl-coenzyme A dehydrogenase deficiency)
      - Mitochondrial disease
    - CNS
      - Trauma
      - Tumor
      - Infection
      - Diencephalic syndrome
      - Rumination
      - Autonomic responses (pain, shock)
      - Anticipatory nausea and vomiting
- Childhood/adolescence—most of these conditions remain considerations, with additional possible causes.
  - GI
    - Appendicitis
    - Food poisoning (staphylococcal, clostridial)
    - Peptic disease
      - Gastritis
      - Duodenitis
      - Ulcer
      - *Helicobacter pylori* infection
    - Trauma
      - Duodenal hematoma
      - Traumatic pancreatitis
      - Perforated bowel
    - Pancreatitis
      - Viral
      - Traumatic
      - Drug induced
      - Cystic fibrosis; cystic fibrosis gene mutation
      - Hyperparathyroidism
      - Hyperlipidemia
      - Organic acidemia
      - Hereditary pancreatitis

  - Gallbladder
    - Cholelithiasis
    - Choledochal cyst
  - Crohn disease
  - Adhesions
    - Congenital
    - Secondary to abdominal surgery
  - Visceral neuropathy or myopathy
  - Superior mesenteric artery syndrome[2]
- Non-GI
  - Medications
    - Anticholinergics
    - Alcohol
    - Idiosyncratic reaction (eg, codeine)
    - Chemotherapy and radiation therapy
    - Overdose (especially aspirin or acetaminophen)
  - CNS
    - Cyclic vomiting
    - Migraine
    - Anorexia nervosa, bulimia nervosa
  - Motion sickness
  - Metabolic
    - Diabetic ketoacidosis
    - Acute intermittent porphyria
  - Pregnancy

LABORATORY EVALUATION

- With persistent vomiting, the clinician should expect to see a metabolic alkalosis.
- Metabolic acidosis raises concerns about underlying metabolic disorder or drug intoxication.

IMAGING

- Evaluation of the GI tract usually includes an upper GI contrast roentgenographic study.
- In an infant between 2 and 12 weeks of age, the first study is often an ultrasound of the abdomen for pyloric stenosis.
- Magnetic resonance imaging is more sensitive than computed tomography of the head if a brain tumor is a consideration in an infant.
  - Further workup for metabolic or neurologic disease should be considered, as appropriate.
- If a midgut volvulus is suspected
  - Plain-film radiography of the abdomen may show a paucity of gas distal to the upper small intestine.
  - An upper GI contrast radiographic study should be done at once with controlled introduction of barium through a nasogastric tube after gastric aspiration.
  - A barium enema investigation of cecal position is less reliable when evaluating a patient for malrotation.
    - Lack of complete correlation of developmental rotation of the cecum with that of the duodenum

DIAGNOSTIC PROCEDURES

- The following tests are all useful in establishing a diagnosis of GER:
  - Esophageal pH monitoring
    - Wireless pH capsule monitoring can be performed in children >2–3 years and is generally well tolerated.
  - Esophageal biopsies
  - Gastroesophageal scintiscan
- Endoscopy is feasible in all children, even newborns, and, when indicated, should be performed by an experienced examiner using a pediatric instrument.

TREATMENT APPROACH

- Acute intercurrent vomiting without serious underlying disease or significant dehydration should be treated by administering clear liquids by mouth, eg, in acute gastroenteritis or otitis media.
  - Start with a period of 4–6 hours without oral intake.
    - Begin with frequent small quantities of clear liquids.
    - 1 teaspoonful every few minutes for infants.
    - Gradually increase volume and extension of the intervening period.
- Patients should be monitored for signs of dehydration.
- If vomiting is associated with diarrhea and dehydration, oral rehydration solution is indicated.
  - Mild to moderate dehydration may be corrected by oral rehydration, even in the presence of ongoing vomiting.
  - Carbonated beverages may increase vomiting.
  - Fluids that tend to slow gastric emptying and should be avoided include
    - High osmolality
    - Long-chain triglycerides
    - Anticholinergic drugs
- Antiemetic drugs
  - Should be avoided in infants but, at times, may be useful in older children.
  - Do not appear to have a role in the management of acute viral gastroenteritis.

- For persistent vomiting, a nasoduodenal infusion may be useful.
- Significant vomiting that requires intravenous fluid therapy is usually associated with hypochloremic alkalosis with secondary hypokalemia.

SPECIFIC TREATMENT

Antiemetics

- Antiemetic drugs used most commonly for acute symptoms are ondansetron and promethazine.
- Rectal suppositories are preferable to oral drugs.
  - Nausea is associated with gastric atony and unpredictable absorption.
- Dopamine-receptor antagonists are effective for chemotherapy-induced vomiting.
  - Metoclopramide.
  - 5-HT_3-receptor antagonists (ondansetron) appear to have even greater efficacy and are without the risks of dystonic reactions associated with metoclopramide.
- Low-dose erythromycin has been used to treat poor gastric emptying when there is not a mechanical obstruction (eg, postviral gastroparesis).

Motion Sickness

- Antihistamines and anticholinergics prevent motion sickness by acting at histamine H_1.
  - Diphenhydramine
  - Dimenhydrinate
  - Meclizine
  - Promethazine
- As do muscarinic cholinergic receptor antagonists.
  - Scopolamine

GER

- Management of GER must be individualized.
- The extent of treatment depends on the volume of emesis and the presence of any of the complications of reflux.
  - Esophagitis with or without esophageal stricture or intractable anemia
  - Failure to thrive
  - Respiratory manifestations
- For infants, medical management includes thickening feeds with cereal.
  - Standard concentration is 1 tablespoonful of cereal for each 1–2 ounces of formula.
- Although prone positioning of young infants reduces reflux, this should only be done when the infant is observed and awake because of a risk of sudden infant death syndrome.
  - Left lateral decubitus positioning is discouraged for sleeping infants because they may become prone.
- Prone positioning may be useful >1 year.
- Elevating the head of the bed remains standard therapy for older children and adults.
- Older children should avoid snacks or liquids after dinner and agents that exacerbate esophagitis, eg, alcohol, caffeine, smoking.
- Medications can be used in an attempt to improve lower esophageal function and gastric emptying.
  - Metoclopramide
  - Baclofen
- Medications also can be used to decrease exposure of the esophageal mucosa to acid.
  - Antacids
  - H_1-receptor blockers
  - Proton pump inhibitors
- A slurry of sucralfate is used occasionally as a cytoprotective agent.
- Medical management may be unsatisfactory.
  - In this case, antireflux surgery, fundoplication, should be considered.
  - In these children, results of surgery are generally good when performed by an experienced surgeon, and benefits can be long-lasting.
  - In children who have psychomotor retardation and GER, antireflux surgery may not eliminate respiratory symptoms.
    - Other factors, such as swallowing dysfunction, may contribute to these findings.
  - Among all children undergoing a Nissen fundoplication, risk of a postoperative complication requiring further surgery may be as high as 10%.
    - Underscores the need for careful patient selection for this operation

Abdominal Migraine

- The following medications are highly effective as prophylactic treatment for abdominal migraine.
  - Cyproheptadine
  - Amitriptyline
  - Topiramate
  - Propranolol
- Treatment success helps confirm the diagnosis.

WHEN TO REFER

- Persistent vomiting
- Recurrent episodes of vomiting
- Vomiting associated with a significant underlying process (eg, surgical abdomen, neurologic problem)

WHEN TO ADMIT

- Intractable vomiting with dehydration
- Vomiting in association with symptoms or signs of
  - Acute abdominal process (eg, acute appendicitis, pancreatitis, cholecystitis)
  - Raised intracranial pressure

FOLLOW-UP

- All patients with vomiting should be followed carefully and monitored for
  - Weight changes
  - Signs of dehydration
  - Electrolyte abnormalities

COMPLICATIONS

- The most significant complications of vomiting include
  - Dehydration and electrolyte imbalance, especially when the vomiting is persistent.
  - Aspiration pneumonia.
  - Hemorrhage from prolapse gastropathy.
    - A hemorrhagic area on the posterior wall of the proximal stomach
  - Less commonly, Mallory-Weiss syndrome, a tear at the gastroesophageal junction.
  - Rupture of the esophagus, very uncommon in children.
  - Feeding refusal may follow persistent vomiting, especially in infants.

PROGNOSIS

- Prognosis depends on the cause of the vomiting.

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DEFINITION

- The definition of significant weight loss varies by the child's age and includes acute and chronic causes.
- Clinically significant weight loss is dependent on age.
  - Newborns may lose 5%–10% of birth weight in the first few days of life; losses >12% are concerning.
  - In children, weight loss >5%–10% from baseline may be concerning.
  - In adolescents, in addition to weight relative to baseline, consider absolute weight in relation to ideal body weight.

HISTORY

- In all patients, records of previous body weights, allowing for differences in weighing technique, can be helpful.
- Obtain a complete history, including
  - Diet and consumption history of child and family, with caloric assessment.
  - Assess parental expectations.
  - Take a careful birth, family, past medical, and medication history.
    - Assess sick contacts/exposure to illness and immediate past history of febrile or other illness.
    - Determine the number of urinations and bowel movements per day.
    - Review gastrointestinal/malabsorption symptoms, such as emesis, constipation, and diarrhea, and amount, frequency, and character of stools.
    - Assess other indications of feeding intolerance, including rashes.
    - Compare caloric intake with estimated caloric needs.
  - For infants
    - In general, an infant should gain 25–30 g each day in the first 3 months of life.
    - Assess feeding effort and coordination.
- If formula-feeding
      - Discuss the proportions in which formula is constituted.
      - Estimate total caloric intake from the volume of formula and caloric density of formula (standard is 20 kcal/oz).
      - The formula-fed newborn rarely loses >5% of birth weight in the first few days.
      - Weight less than birth weight at the age of 10 days is unusual for a formula-fed neonate and indicates need for thorough evaluation.
    - If breastfeeding, assess
      - Perceived adequacy of maternal milk production.
      - Ability of infant to breastfeed.
      - Typically, birth weight is regained in 10 days; consider interventions if it is unlikely to be regained in the first 2 weeks, especially with new parents.
  - For children and adolescents
    - Discuss whether eating leads to symptoms, such as pain, emesis, diarrhea, or fatigue.
    - Discuss quantity and type of stools.
    - Assess body image, social context (including family function and patient's emotional well-being), and stressors.
    - Consider HEADDSSS (**h**ome environment, **e**ducation and employment, **e**ating, peer-related **a**ctivities, **d**rugs, **s**exuality, **s**uicide/depression, and **s**afety from injury and violence) examination and substance abuse.
    - Does the patient participate in sports where weight loss is a goal?
      - Wrestling, gymnastics, ice-skating, running, swimming, diving, dancing.
      - If yes, obtain a thorough dietary and supplement history.
    - For girls, obtain a menstruation history.

PHYSICAL EXAMINATION

- Subjective impressions of weight loss should be verified objectively before an evaluation is undertaken.
  - True weight loss may sometimes be difficult to differentiate from factitious weight loss.
  - Errors occur in 5%–20% of all children weighed because of faulty equipment or poor technique.
  - Weigh the patient and plot on growth chart; consider serial weights for computation of growth velocity.
  - Consider weighing a breastfed infant before and after a feeding.
  - Measure length/height.
    - In children ≥2 years, compute body mass index, body mass index percentile, and weight for height.
- Vital signs.
  - Assess temperature; consider heart rate, blood pressure, and orthostatic vital signs.

- Physical examination.
  - Assess mental status.
  - Assess volume status and for anemia (eg, pale conjunctivae).
  - Examine oral mucosa for thrush and ulcerations.
    - Oral aphthous ulcers may be related to Crohn disease.
    - Discoloration of teeth may be related to purging behaviors.
  - Assess cardiorespiratory status.
  - Assess abdomen and for presence of organomegaly.
  - Look for signs of malnutrition or vitamin deficiencies (eg, lanugo).
  - Assess for toxidromes in adolescents.
- In breastfed infants, where weight loss is suspected because of inadequacy of feeding, observe the mother nursing the baby.
  - The infant should be observed to latch on to the breast correctly.
    - Note whether there is loud swallowing or occasional choking at the start of feeding.

DIFFERENTIAL DIAGNOSIS

- The differential diagnosis for weight loss is broad and varies somewhat with age.
- Of note, poverty is the greatest single risk factor for failure to thrive in the United States.
- Psychosocial factors (eg, poor parent-child interaction, depression, rumination) often underlie poor growth and development.
  - Actual weight loss is much less common in this setting than slowdown or cessation of weight gain and linear growth.
  - Psychosocial dysfunction that results in a child's weight loss requires a prompt and thorough evaluation.
  - Eating disorders have been described in prepubertal children as young as 7 years.

Newborns and Young Infants

- Difficulties in establishing breastfeeding
- Inappropriate dilution or choice of formula
- Inadequate intake
  - In breastfed infants, inadequate intake at the breast is the most common reason for weight loss.
  - In formula-fed infants, consider unsuccessful feeding related to parental inexperience; if this is not the case
    - Search for an organic problem.
    - Evaluate family dynamics, support mechanisms, and adjustment to the newborn.
- Excessive losses from vomiting or diarrhea
  - With vomiting, consider gastrointestinal malformations (eg, pyloric stenosis, duodenal atresia).
- Infection
- Metabolic abnormality
- Craniofacial abnormalities
- Central nervous system dysfunction
- Somnolence from maternal medications or substance abuse
- Maternal depression, inexperience, lack of knowledge
- Congenital heart disease
- Polyuria (eg, diabetes insipidus, renal disease)

Older Infants, Preschoolers, and School-aged Children

- Inadequate intake
  - Poverty
  - Psychosocial dysfunction (failure to thrive)
    - Neglect
    - Parental depression
    - Childhood depression
  - Loss of appetite
    - Underlying illness
      - Acute (eg, otitis media)
      - Chronic (eg, malignancy)
    - Medication effect
  - Childhood eating disorder
- Excessive losses
  - Vomiting
  - Diarrhea
  - Gastroesophageal reflux
  - Rumination
- Poor utilization (eg, malabsorption syndromes)
- Increased need
  - Fever and infection
  - Chronic illness (eg, congenital heart disease)
  - Excessive activity
- Chronic illness with compound mechanisms
  - Cystic fibrosis
  - Diabetes mellitus
  - Inflammatory bowel disease
  - Immunodeficiency disorders, especially HIV infection
  - Tuberculosis
- Surgery

Adolescents

- Dieting behavior
- Adolescent eating disorders
  - Anorexia nervosa
    - Suspect when the adolescent is unwilling or unable to maintain body weight over a minimally normal weight for age and height.
    - Attitudes and behaviors about eating or body image are distorted; amenorrhea, emaciation, and overactivity may be described.
    - Concurrently, may have hypothyroidism, bradycardia, hypothermia, or growth of lanugo-like hair on body and extremities.
  - Bulimia nervosa
    - Binge eating, followed by self-induced vomiting, self-starvation, overactivity, and use of cathartics or diuretics to reduce weight
      - These behaviors are practiced in secret, and the adolescent often denies them.
  - Other eating disorders
- Psychiatric affective disorders, especially depression
- Malignancy, especially lymphoma
- Inflammatory bowel disease
- Diabetes mellitus
- Hyperthyroidism
- Tuberculosis
- Sports-related weight loss
  - Adolescents may engage in unhealthy weight-control practices to seek advantage in their athletic activities.
    - These may include food restriction, vomiting, overexercise, diet pills, stimulants, insulin, nicotine, and voluntary dehydration.

LABORATORY EVALUATION

- Evaluation is guided by clinical suspicion.
- In infants, ensure that newborn screening has been performed.
- Studies may include
  - Blood chemistries, kidney function tests
  - Complete blood cell count, smear
  - Erythrocyte sedimentation rate
  - Serum protein and albumin levels; serum carotene; specific tests of malabsorption
  - Tuberculosis skin test
  - Stool guaiac
  - Urinalysis, including specific gravity; urine culture
- Please also refer to the Laboratory Evaluation section of Loss of Appetite (on anorexia).

IMAGING

- Imaging is guided by clinical suspicion.

DIAGNOSTIC PROCEDURES

- Diagnostic procedures may be performed as guided by clinical suspicion.
  - Upper endoscopy with biopsy
  - Colonoscopy
  - Sweat chloride testing
  - Esophageal motility testing
  - pH probes

TREATMENT APPROACH

- In addition to diagnostic testing, serial evaluations of weight and intake are the cornerstones of assessing weight issues.

SPECIFIC TREATMENT

- See Loss of Appetite (anorexia), Anorexia Nervosa, and Bulimia Nervosa.

Infants

- In breastfed infants with inadequate weight gain, support and education are appropriate interventions.
- Appropriate weight gain in the following few days provides evidence that the infant is well and confirms the diagnosis of initial underfeeding.
- Prematurely recommending discontinuation of breastfeeding is inappropriate.
  - The mother's motivation to breastfeed and her positive or negative feelings about the experience should be discussed.
  - Encouragement and support should be given for continuation of nursing.
  - Do not reinforce parental perceptions that the mother's milk supply is insufficient or less nutritious than formula.
  - Lactation consultants or community organizations (eg, La Leche League) may be helpful in supporting lactation efforts.
  - Infants who fail to thrive while breastfeeding require more intensive nutritional rehabilitation while still preserving breastfeeding.

WHEN TO REFER

- Refer when there is evidence or suspicion of
  - Malignancy
  - Endocrinopathy (thyroid, adrenal, pituitary)
  - Gastrointestinal disorder (eg, gastroesophageal reflux disease; malabsorption, including cystic fibrosis; inflammatory bowel disease)

- Pancreatitis
- Heart disease
- Renal disease
- Pulmonary disease
- Rheumatologic condition
- Central nervous system abnormality
- Metabolic disorder
- Surgical abdominal problem (eg, pyloric stenosis, Hirschsprung disease, volvulus)
- Immunodeficiency
- Unusual infection
- Psychiatric diagnosis in child or caregiver
- Anorexia nervosa or bulimia nervosa in the child or adolescent

WHEN TO ADMIT

- A newborn, when
  - Weight loss cannot be managed as outpatient.
  - Weight loss is >12%–15% of birth weight.
  - Excessive fluid loss (eg, vomiting, diarrhea, polyuria).
  - Evidence of infant hypernatremic dehydration.
  - Suspicion of infection, metabolic abnormality, congenital heart disease, other conditions requiring evaluation.
  - Extreme passivity of the infant, which may require tube feeding.
  - Need for intensive maternal education and support.
- At any age, when
  - Weight loss is excessive (>5%–10% of previous weight).
  - Excessive fluid loss from vomiting or diarrhea.
  - New onset of diabetes mellitus (usually).
  - Evidence of severe febrile illness (eg, pneumonia, pyelonephritis, osteomyelitis, meningitis, septic arthritis).
  - Evidence of dehydration.
  - Physiological instability.
  - Severe bradycardia.
  - Hypotension.
  - Hypothermia.
  - Orthostatic changes.
  - Electrolyte abnormalities (eg, hypernatremia, hypokalemia).
  - Evidence of significant psychosocial dysfunction.
- An adolescent, when
  - Eating disorder cannot be managed as outpatient.
  - Severe malnutrition, with weight <75% of ideal body weight.
  - Evidence of dehydration or electrolyte abnormalities.
  - Physiologic instability.
  - Acute food refusal.
  - Uncontrollable binge eating and purging.
  - Acute medical complication of malnutrition (syncope, seizures, cardiac failure, pancreatitis).
  - Suicidal intent or ideation or psychosis.

Wheezing

DEFINITION

- *Wheezing* is a continuous, musical sound that represents turbulent, intrathoracic airflow.
- It is usually more prominent during expiration but may also be present in inspiration.

HISTORY

- A detailed and focused history can often provide clues to an accurate diagnosis.
- History includes
  - Age at onset
  - Frequency of wheezing
  - Intermittent or constant wheezing
  - Recent upper respiratory illness and fever
  - Association with vigorous activity, changing weather, exposure to allergens
  - Acuteness of onset
  - Accompanying coughing, choking
  - Frequent vomiting
  - Positional wheezing
  - Worsening with agitation or crying
  - Difficulty swallowing
  - Failure to thrive
  - Hemoptysis
  - Recent surgical procedure/intubation
  - Poor response to conventional therapy
  - Family history

PHYSICAL EXAMINATION

- Through auscultation, determine if wheezing is bilateral or unilateral.
- Unilateral wheezing.
  - Most often associated with aspiration of a foreign body
  - Can accompany unilateral bronchial compression or stenosis
- Make a detailed assessment of the auditory characteristics of the wheeze.
  - Can help determine whether the obstruction is central or peripheral.
    - Wheezing that varies in pitch and can be heard throughout the chest (musical, heterophonous) typically represents small airway obstruction.
    - Wheezing that is more even in pitch (monophonic, homophonous) is typically central airway obstruction and can often be heard best in central locations, such as the sternal notch.
    - May be unreliable in a small infant
  - Large airway obstruction is more likely to be heard throughout the entire expiratory phase.
- Positional characteristics should be evaluated.
  - Wheezing caused by a dynamic lesion (eg, tracheomalacia) is often worse when a patient is supine.
  - Mediastinal structures, such as the heart and the great vessels
    - Tend to fall posteriorly in the supine position and can be obstructive.
    - Fall anteriorly when the patient is prone, relieving pressure on the airway and improving the wheeze.
  - Wheezing caused by small airway obstruction or fixed compression of a large airway does not typically change with position.

DIFFERENTIAL DIAGNOSIS

- Any process that can cause obstruction of intrathoracic airways should be considered in the differential diagnosis.
- Viral bronchiolitis and asthma account for most wheezing.
- Wheezing after a recent surgical procedure or intubation suggests acquired obstruction.
- Distinguishing large airway obstruction (ie, trachea or main stem bronchi) from peripheral small airway obstruction (ie, asthma) is difficult because both can cause expiratory wheeze.
- Asthma.
  - Worse with exercise or respiratory infections
  - Responds to bronchodilators and steroids
  - Reversible obstruction on pulmonary function testing
  - Heterophonous wheeze
  - Positive bronchial challenge (bronchoprovocation)
  - Family history
- Tracheomalacia.
  - Worse with activity or agitation
  - Poor response to bronchodilators and steroids
  - Homophonous wheeze
  - Airway collapse on fluoroscopy
  - Collapsible trachea on bronchoscopy
- Bronchomalacia.
  - Worse with activity or agitation
  - Poor response to bronchodilators and steroids
  - Homophonous wheeze
  - Airway collapse on fluoroscopy
  - Collapsible bronchus on bronchoscopy

- Foreign body.
  - Sudden onset.
  - May have a history of choking, but many patients with foreign body aspiration will not have an obvious history.
    - Choking should be suspected even in a child whose wheezing has been present for days or weeks.
  - Differential breath sounds.
  - Differential hyperinflation or collapse on radiography.
- Heart failure or pulmonary edema.
  - Poor response to albuterol
  - Poor growth
  - Hepatomegaly
  - Radiography showing increased fluid
  - Responds to diuresis
- Bronchiolitis.
  - Infant: upper respiratory infection symptoms
  - Positive viral studies
  - Wheezing caused by viral bronchiolitis
    - Is usually preceded by upper respiratory symptoms and fever
    - Worsens within the first few days of onset
    - Tends to improve slowly thereafter
- Vocal cord dysfunction.
  - Poor response to all therapies
  - Severe distress reported
  - Pulmonary function tests: normal or with abnormal inspiratory loop
  - Laryngoscopy: vocal cord adduction during inspiration
- Cystic fibrosis.
  - Poor growth, gastrointestinal (GI) symptoms
  - Recurrent pneumonias
  - Positive sweat test
- Gastroesophageal reflux and aspiration.
  - Variable response to bronchodilators
  - Often worse after meals
  - Poor growth, GI symptoms
  - Recurrent pneumonias
  - Positive reflux evaluation (upper GI, nuclear scan, or pH probe)
- Pulmonary hemosiderosis.
  - Rare disorder causing anemia and recurrent wheezing from blood irritating the peripheral airways
- Vascular compression.
  - Central wheeze
  - No bronchodilator response
  - Indentation on esophagram
  - Anatomy demonstrated on thoracic magnetic resonance imaging (MRI)
- Large airway abnormality (stenosis, complete rings, compression).
  - No response to therapy
  - Worse with activity
  - Stridor noted at times
  - Flattened or square flow–volume loop
  - Obstruction visible on imaging or bronchoscopy
- Wheezing that appears at birth or soon afterward should prompt an evaluation for congenital airway abnormalities, such as
  - Tracheomalacia
  - Complete rings
  - Vascular abnormalities or compression

LABORATORY EVALUATION

- Laboratory testing may be indicated to diagnose specific clinical entities.
  - Sweat test for cystic fibrosis.
  - Viral studies can identify respiratory syncytial virus or influenza.

IMAGING

- Chest radiography can be used to detect
  - Thoracic masses that cause obstruction of airways
  - Foreign body aspiration
- Airway fluoroscopy
  - Can confirm diagnosis and help quantify the severity of tracheobronchomalacia
- Esophagography or upper GI series
  - Useful if a vascular abnormality is suspected
- Computed tomography or MRI
  - Confirmation of vascular abnormality
- 3-dimensional airway reconstruction
  - High radiation dose should limit use.

DIAGNOSTIC PROCEDURES

- Pulmonary function testing can help
  - Characterize a wheeze objectively in patients >5 or 6 years.
  - Distinguish reversible from fixed obstruction.
  - Distinguish small airway from large airway obstruction.
- Direct visualization of the airway via flexible bronchoscopy
  - To characterize dynamic lesions (ie, tracheobronchomalacia)
- Rigid bronchoscopy
  - Can be useful in diagnosis and treatment of tracheal stenosis

TREATMENT APPROACH

- In general, when evaluating and managing the wheezing child
  - Be aware of the various clinical entities that can produce wheezing.
  - Be able to recognize by history and physical examination patients who require further workup.
  - Initiate simple diagnostic tests.

SPECIFIC TREATMENT

Asthma and Viral Bronchiolitis

- The 2 most common causes of wheezing in pediatric patients.
- See Asthma.
  - Responds to bronchodilators
  - Responds to steroids
- See Bronchiolitis.
  - No evidence supports the regular use of β-agonist therapy in viral bronchiolitis.
  - Hypertonic 3% saline has been used as adjunctive therapy in hospitalized patients.
- Some children require hospitalization for severe respiratory distress, hypoxemia, poor feeding, or dehydration.

WHEN TO REFER

- Refer children with unusual presentations or poor response to conventional therapies to appropriate subspecialty physicians.
  - Persistent or recurrent wheezing in an infant <1 year
  - Apparent paradoxical response to bronchodilators
  - Poor weight gain or growth associated with chronic or recurrent wheezing
  - Repeated hospitalization or multiple courses of oral corticosteroid
  - Persistent asymmetric wheezing

WHEN TO ADMIT

- Respiratory distress unresponsive to therapy
- Hypoxemia
- Tachypnea interfering with ability to eat or drink
- Altered mental status or signs of fatigue

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